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EDITORIAL

REVIEW ARTICLE

ORIGINAL ARTICLES

CASE REPORTS

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KUWAIT MEDICAL JOURNAL (KMJ)
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INTRODUCTION

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AIMS AND SCOPE

KMJ aims to publish peer-reviewed manuscripts of international interest. Submissions on clinical, scientific or laboratory investigations of relevance to medicine and health science come within the scope of its publication. Original articles, case reports, brief communications, book reviews, insights and letters to the editor are all considered. Review articles are solicited. Basic medical science articles are published under the section 'Experimental Medicine'.

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Burrows B, Lebowitz MD. The β agonists dilemma (editorial). N Engl J Med 1992; 326:560-561.

Book

Roberts NK. The cardiac conducting system and His bundle electrogram. New York, Appleton-Century-Crofts, 1981; 49-56.

Book chapter

Philips SJ, Whisnam JP. Hypertension and stroke, In: Laragh JH, Bremner BM, editors. Hypertension: pathophysiology, diagnosis, and management. 2nd Ed. New York: Raven Press; 1995. p 465-478.

Weblinks

U.S. positions on selected issues at the third negotiating session of the Framework Convention on Tobacco Control. Washington, D.C.: Committee on Government Reform, 2002. (Accessed June 4, 2003, at http://www.house.gov/reform/min/inves.tobacco/index_accord.htm.)

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Editorial

All Great Truths Begin as Blasphemies

Belle M Hegde
The Journal of the Science of Healing Outcomes, State College, Pennsylvania, USA and Mangalore, India*
Manipal University, Manipal India**
The Middlesex Medical School, University of London, UK#
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"It is only those who are in constant revolt that discover what is true, not the man who conforms, who follows some tradition. It is only when you are constantly inquiring, constantly observing, constantly learning, that you find truth, God, or love."

Jiddu Krishnamurthi, Think on These Things

Bernard Shaw was right when he wrote the above caption. I have become so unpopular in my own profession. I thought I was telling the simple truths that occurred to me in my day to day bedside experiences in all my articles and speeches. People blame me for every article that I write. "Truth is like the town whore. Everybody knows her, but nonetheless, it's embarrassing to meet her on the street," wrote Wolfgang Borchert years ago. Medical fraternity and business try their best to suppress the truth to the extent possible. Many of my professional brethren are not to blame. They follow their medical school teaching and the plethora of "scientific" literature to the letter. Unfortunately, most of those data are doctored to suit the vested interests in the name of science. They want to sell the idea that every ill has a pill or an operation; which is not true. The claptrap and the schooling of society on those lines has been very effective in that it is almost impossible to convince a patient and/or his doctor today that the patient's illness does not require any outside intervention in the majority of cases except his/her own inner handyman, the immune system, to be aroused.

I feel so relieved today that a new study, published in one of the leading medical research journals, The Journal of Translational Medicine, showed that almost all randomized controlled trials (RCTs) have been seriously flawed and that their conclusions can not be relied upon! (Sci Tranl Med 2011; 3:70. DOI 10.1126 / translmed 3001244). This boils down to the simple truth that reductionist scientific base of modern medicine, so called evidence based medicine (EBM), is only a myth. The study elegantly showed that what helps patients at the end of the day is their faith in the treatment that the doctor gives-the placebo effect. This puts the onus of patient care on the treating physician. We have come one full circle from the time Robert Hutchinson wrote that medical consultation is that vital meeting between two human beings - the patient and his/her physician. It is the faith that the former has in the latter that works. The present study, which you are going to read in detail below, has made use of some of the most sophisticated scientific methodologies to show that it is the faith that does the trick.

What we want are good human beings as doctors and not their numbers. A doctor, following any one of the many systems of medical care prevalent in the world, is as good as any other, if only he/she is a good human being who has the ultimate good of his/her patients at heart. We do not need more doctors by number but more good human beings as doctors. In fact, if one cares to count, we have more doctors per capita in many parts of the world. Many systems of medicine are being practised from time immemorial and all of them did what modern medicine was supposed to do as per Hippocratic pronouncements: "cure rarely, comfort mostly, but console always." The two most powerful drugs that

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mankind ever produced are the two kind words of a doctor!

It is only in the last one century that the western modern medicine was thrust upon the populace as the best and the rest of them were condemned as unscientific. If one goes through the history of medicine one quickly realizes the politics of this exercise. The Abraham Flexner report of 1910 classified scientific medicine as the one using reductionist chemicals and the rest as unscientific. There were many systems of medicine in North America at that time. It is worth noting that Flexner was only a high school headmaster who was given this task. The next is the Benedict Fitzgerald report 1953 in the USA which showed how modern medical establishment tried to suppress the truth about the efficacy of alternate systems in the treatment of cancer. It was in the year 1899 that Chiropractic was almost banned from the US. The trend is reversing now for the good of humanity. Ibn Siena, a great Arabic physician had given many methods of medical care which were very useful.

Even as far as forty years ago, WHO had done an exercise to see the effect of five systems of medicine prevalent at that time in Thailand. The prospective study did show that all systems were equally effective. That was an observational study. The present science amply supports that data. In addition, a fourteen country study recently showed that where there were more doctors per capita, the health status of society was the worse compared to the countries with lesser numbers of doctors per capita. The study also showed that if the number of doctors with sub specialization was higher vis-à-vis humane family doctors, health status was worse. Japan with the lowest specialists among the fourteen countries had the best health status, least illness incidence and highest longevity of the populace![1]

Drs. Bingel and colleagues, working from Oxford, Cambridge, Munich, and Hamburg did demonstrate the effect of the "expectation effect" on drug therapy, which in their own words goes thus: "Evidence from behavioral and self-reported data suggests that the patients' beliefs and expectations can shape both therapeutic and adverse effects of any given drug. We investigated how divergent expectancies alter the analgesic efficacy of a potent opioid in healthy volunteers by using brain imaging. The effect of a fixed concentration of the μ-opioid agonist remifentanil on constant heat pain was assessed under three experimental conditions using a within-subject design: with no expectation of analgesia, with expectancy of a positive analgesic effect, and with negative expectancy of analgesia" (that is, expectation of hyperalgesia or exacerbation of pain). They used functional magnetic resonance imaging to record brain activity to corroborate the effects of expectations on the analgesic efficacy of the pain modulatory system, and the negative expectancy effects with activity in the hippocampus. On the basis of subjective and objective evidence, they contended that an individual's expectation of a drug's effect critically helped him/her. Positive treatment expectancy substantially enhanced (doubled) the analgesic benefit of remifentanil. In contrast, negative treatment expectancy abolished remifentanil analgesia. These subjective effects were substantiated by significant changes in the neural activity in brain regions involved with the coding of pain intensity. The positive expectancy effects were associated with activity in the endogenous influences on its therapeutic efficacy and those regulatory brain mechanisms differ as a function of expectancy. They proposed that it may be necessary to integrate patients' beliefs and expectations into drug treatment regimes alongside traditional considerations in order to optimize treatment outcomes.[2]

Talking to the BBC, Professor Irene Tracey from Oxford University said, "It's phenomenal, it's really cool. It's one of the best analgesics we have and the brain's influence can either vastly increase its effect, or completely remove it." (http://www.bbc.co.uk/news/health-12...). As pointed out by George Lewith, a professor of health research at the University of Southampton, these findings call into question the scientific validity of many randomized clinical trials. He said, "It completely blows cold randomized clinical trials, which don't take into account expectation." (http://www.naturalnews.com/031451_drug_trials_placebo_effect.html#ixzz1ES4z9KmM)

There are two kinds of doctors. The placebo doctors are the ones that generate a positive mental attitude towards treatment in a patient while the nocebo doctors create the opposite effect. They scare the patient away to begin with thanks to their wrong deterministic future predictions like "you have six months to live" etc. No one can predict the future as the future is yet to be born and to predict that in any dynamic system we must have the complete knowledge of the initial state of the organism. Even to predict the future of this globe, one has to have all the information about its initial state - impossibility. Albert Einstein rightly said that "all complicated problems in this universe have very simple solutions". Medical care looks simple if only we cater to the mind of the patient. Mind and

body being but one single entity, patient care boils down to caring for the patient. We need to de-school society and doctors to develop the placebo trait in them.

It is better to end this with a quote from Winston Churchill: "The truth is incontrovertible, malice may attack it, ignorance may deride it, but in the end; there it is." We need doctors to guide every patient in the right path. Authenticity should be their goal and compassion their path. *'Vaidyo Naarayano Harihi'* (Doctor is the God incarnate). Some of our great brains in the past had predicted this. "If the whole materia medica could be sunk to the bottom of the seas, it will be that much worse for fishes and that much better for mankind," wrote Oliver Wendell Holmes. "More people make a living off hypertension than dying of it", wrote Sir George Pickering. "Patient care is CARING for the patient", wrote Sir Francis Peabody. Two most powerful drugs ever invented by man are the two kind words of a caring doctor. Long live doctoring.

"Truth is the property of no individual but is the treasure of all men."

Ralph Waldo Emerson

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Review Article

Non-culture-Based Diagnostic Methods for the Diagnosis of Invasive Candidiasis: Are They Helpful to Clinicians?

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Department of Microbiology, Faculty of Medicine, Kuwait University, Kuwait

Kuwait Medical Journal 2013; 45 (1): 4 - 14

ABSTRACT

Invasive candidiasis in immune-compromised patients is associated with high attributable mortality. Early detection of candidemia and accurate identification of *Candida* species are essential pre-requisites for improved prognosis. Since clinical presentation is non-specific and blood culture-based methods lack sensitivity, detection of immunological and molecular markers has provided an alternative for early diagnosis of invasive candidiasis. Serial estimations of these biomarkers have also proved useful to initiate pre-emptive therapy in suspected patients before clinical signs appear and to monitor response to therapy. Antigen-based methods include detection of β-D-glucan (panfungal marker) and *Candida* mannan (genus-specific marker). Detection of both, *Candida* mannan and anti-mannan antibodies has higher sensitivity. While false positive / negative results remain a problem, these markers provide a useful adjunct to the diagnosis if performed in select patient population. Recent advances have also been made in nucleic acid-based detection methods. A commercial real-time PCR assay (LightCycler SeptiFast) for detection of clinically important *Candida* spp. in blood specimens within six hours is now available. Molecular methods have also resulted in species-specific identification of yeast isolates within an hour. While these advances aid in early and specific diagnosis of candidemia and invasive candidiasis, further evaluation of these approaches in different clinical settings is also needed.

KEY WORDS: Candidemia, *Candida* DNA, *Candida* mannan, β-D-glucan

INTRODUCTION

The last few decades have witnessed the emergence of invasive fungal infections as a major cause of morbidity and mortality in immune-compromised individuals. Although many fungal pathogens are involved, *Candida* spp. play a dominant role, particularly afflicting patients admitted to intensive care units (ICUs)[1]. The incidence of candidemia and invasive candidiasis is also rising due to increasing complexity of surgical procedures, prolonged survival of critically ill patients and increasing use of invasive procedures, intravenous catheters and intravenous hyperalimentation[2]. Blood culture positivity for *Candida* spp. increased from 8% in 1995 to 12% in 2002[3]. During 2006 - 2007, *Candida* spp. were among the fourth most common cause of hospital-associated infections and catheter-associated urinary tract and bloodstream infections[4]. Nearly 90% of invasive *Candida* infections are caused by only four species or species complexes which include *Candida albicans*, *Candida glabrata*, *Candida parapsilosis*, and *Candida tropicalis*[3-6]. Contribution of other *Candida* spp. is minor. However, mini-outbreaks caused by some species (*Candida haemulonii*, *Candida guilliermondii etc.*) have occasionally been recorded among select patient populations[6-9].

The origin of nosocomial *Candida* infections are mostly endogenous from the patient's own flora or occasionally exogenous that are acquired from contaminated biomedical devices, infusates, or hands of healthcare staff[10]. The most common pathogenic *Candida* species is *C. albicans* which is also a predominant component of human microbiota, occurring normally on skin and mucosal surfaces. Bloodstream infections caused by non-albicans *Candida* spp. have also increased in recent years accounting for up to 60% of all episodes of candidemia or invasive candidiasis in some centers[11-13]. Since *C. albicans* is highly susceptible to azole antifungal drugs, widespread use of azoles may have partly contributed to this change in epidemiology of *Candida* infections[14]. However, other factors may also have contributed to this changing epidemiology of *Candida* infections.

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Despite widespread use of fluconazole in clinical practice, the vast majority of *C. albicans* isolates remain susceptible to this drug. However, there is a widely held view that prior exposure to fluconazole is the single most important factor leading to fungemia caused by less susceptible non-albicans *Candida* species, such as *C. glabrata* and *C. krusei*[6,14-16]. Since fluconazole is the mainstay of anti-*Candida* therapy and prophylaxis in resource-limited countries of Asia and Africa, the threat of emergence of resistance is a real possibility. In this context, the recent recognition of a *C. glabrata* phenotype resistant to azoles and echinocandins occurring in ICU and non-ICU settings is a worrisome development[17]. According to ARTEMIS DISK Global Antifungal Surveillance study (1997 - 2005), the overall prevalence of fluconazole resistant isolates was reported as 0.9% for *C. albicans* (n = 18,125), 13.5% for *C. glabrata* (n = 3368), and 8.1% (n = 3120) for *C. tropicalis*[5]. The candidemia caused by non-albicans *Candida* spp. exhibiting reduced *in vitro* susceptibility to azoles poses therapeutic challenges. The introduction of echinocandins has proven to be highly effective against *Candida* spp. isolates with reduced susceptibility to azoles[18]. Although, some reports have suggested that *C. parapsilosis* complex species are relatively less susceptible than other *Candida* spp. in *in vitro* studies. However, all three echinocandins have been used for the treatment of mucosal and invasive candidiasis with favorable outcomes and with few side effects[18-20].

Apart from the differences that exist in antifungal susceptibilities of individual *Candida* species, there are also host-related preferences. *Candida* parapsilosis is the second most important cause of candidemia in East / Southeast Asia and Middle East, particularly affecting pediatric patients in association with intravenous catheters[5,21,22]. *C. tropicalis* may be seen more frequently among neutropenic patients with prolonged stay in ICU[23] while *C. glabrata* and *C. krusei* may occur more commonly among elderly hematologic patients receiving fluconazole prophylaxis[24]. Like-wise, attributable mortality in candidemia is also variable, being lowest for cases caused by *C. parapsilosis* (30%) and highest for cases caused by *C. krusei* (59%)[3,12].

Since invasive candidiasis cause significant mortality and antifungal susceptibility profiles are variable, rapid diagnosis and species-specific identification are crucial for timely administration of appropriate antifungal treatment[18]. Although blood culture is the gold standard for the diagnosis of candidemia, it takes a minimum of 24 - 48 hours to become positive and at least a week to determine that a specimen is culture-negative[25]. Moreover, even after obtaining blood culture result, species-specific identification of different *Candida* spp. by conventional methods is time-consuming as these methods principally rely on phenotypic characteristics (morphologic and biochemical tests) which lack sensitivity. Thus many closely related species (*C. albicans* / *C. dubliniensis*, *C. parapsilosis* /*C. orthopsilosis* / *C. metapsilosis* and *C. glabrata* / *C. nivariensis* / *C. bracarensis*) may be misidentified due to indistinguishable physiological characteristics[26-29].

Recent studies have shown that a delay of each day in initiating antifungal (mainly fluconazole) therapy after first blood culture has become positive increases the risk of mortality significantly[18,30]. Thus, the risk of mortality was 15% if antifungal treatment was started on the same day when blood cultures became positive, which increased to 24%, 37%, and 40% with initiation of treatment after day 1, 2, and > 3, respectively[30]. In this context, the non-culture based methods offer an attractive alternative for a rapid diagnosis of invasive candidiasis. While these methods have the potential to overcome the limitations of low blood culture positivity (< 50% even in autopsy-proven cases of candidiasis)[31], they also provide a window of opportunity to initiate preemptive antifungal therapy even before signs and symptoms of clinical disease (which are often non-specific) appear[32-34]. The PCR-based methods hold the promise to simultaneously detect and / or identify causative *Candida* species in serum and / or blood samples. Concomitant detection of more than one biomarker is helpful in excluding false positive/ negative results as well as to monitor response to therapy. Here, we present an overview of the recent advances that have been made in this direction using antigen, antibody and molecular approaches.

ANTIGEN-BASED DETECTION OF CANDIDEMIA AND INVASIVE CANDIDIASIS

Two antigen-based tests are currently available for predicting the onset of candidemia in susceptible human host. The 1,3-β-D-glucan (BDG) is an important component of the cell wall of most fungi that is released in serum samples during fungal infections. An antigen-based test that detects the presence of BDG is approved by Food and Drug Administration (FDA) of the United States of America and European Organization for Research and Treatment of Cancer/ Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) for the diagnosis of candidemia and other invasive fungal infections[25,32]. The test is commercially available from at least four manufacturers with the Fungitell (associates of Cape Cod Inc., East Falmouth, MA, USA) and Wako-Maruha (Wako Pure Chemical Industries Ltd., Tokyo, Japan) assays being more popular. The test has been evaluated mostly among ICU patients with sensitivity values of 64 - 100% and 50 - 55% and

Table 1: Performance of commercially available antigen- and antibody-based assays for the diagnosis of candidemia and invasive candidiasis

Commercial assay	Antigen or antibody detected	Sensitivity %	Specificity %
Fungitell	1,3-β-D glucan	64 - 100	45 - 90
Wako-Maruha	1,3-β-D glucan	50 - 55	45 - 90
Platelia Candida Ag	Mannan	53 - 62	91 - 94
Platelia Candida Ab	Anti-mannan antibodies	54 - 65	79 - 87
Platelia Candida Ag + Ab	Mannan + anti-mannan antibodies	79 - 87	82 - 90
C. albicans IFA IgG	*C. albicans* germ tubes antibodies	77 - 89	91 - 100

*Values for sensitivity and specificity are based on several published studies

specificity values of 15 - 90% and 89 - 98% for Fungitell and Wako assays, respectively, for subjects with proven or probable invasive fungal infections (Table 1)[32, 35-41]. The test is applied twice weekly and a single positive test is indicative of infection. Since BDG is a pan-fungal marker, invasive infections suggested by a positive test must be assessed later by radiological and microbiological methods. True positive cases usually show falling BDG titers that eventually become negative in patients responding to antifungal treatment while this trend is not observed in patients not responding to therapy[34,39,42-45]. False positive results due to several conditions, such as hemodialysis (cellulose membrane), cirrhosis, abdominal surgery (glucan containing gauze), treatment with β-lactam antibiotics or immunoglobulins and presence of bacterial endotoxins (lipopolysaccharide) due to Gram-negative bacteremia make its application in clinical setting rather difficult[44,45]. However, based on excellent negative predictive value of this test (approaching 100%), lack of BDG detection is most useful for excluding invasive fungal infection[34,44,45]. Also, colonization of individuals with *Candida* spp. has no apparent effect on the diagnostic performance of the BDG test[32,34,38,46,47].

Another antigen-based test detects the presence of mannan, a polysaccharide which is also a major component of *Candida* cell wall accounting for up to 7% of total dry cell weight. Mannan is also released in blood circulation during infection. The Platelia *Candida* Ag test (Bio-Rad Laboratories, Marnes-la-Coquette, France) detects the presence of mannan in blood (serum) samples in ELISA format[48]. Several retrospective and prospective studies have evaluated the utility of mannan detection for the diagnosis of invasive candidiasis in hematological and ICU patients with sensitivity values of 53 - 62% and specificity of 91 - 94% (Table 1)[46,48-51]. The sensitivity of the test seems to vary with the infecting *Candida* species, being highest for *C. albicans*[51]. A positive test has been recorded several days before radiological detection of hepato-spleenic candidiasis or positive blood cultures[51]. In high risk patients, the test is recommended to be carried out 2 - 3 times per week since presence of mannan in blood is short-lived due to rapid clearance during each episode of candidemia with concomitant appearance of anti-mannan antibodies[33]. Recent studies have demonstrated an increased sensitivity of this test when combined with detection of anti-mannan antibodies in critical but not in immuno-compromised patients.

ANTIBODY-BASED DETECTION OF CANDIDEMIA AND INVASIVE CANDIDIASIS

Two antibody-based tests are also available for the diagnosis of candidemia and invasive candidiasis[33]. Anti-mannan antibodies develop in patients when mannan disappears after an episode of candidemia. An ELISA-based test for the detection of anti-mannan antibodies is marketed as Platelia *Candida* Antibody (Bio-Rad Laboratories, Marnes-la-Coquette, France). The sensitivity of anti-mannan antibody test in several studies (including hematological and ICU patients) has been reported as 54 - 65% with a specificity values ranging from 79 - 87% (Table 1)[33,46,48,51]. However, when the test was combined with simultaneous detection of mannan antigen, the sensitivity (79 - 87%) and specificity (82 – 90%) values improved considerably, both in hematological and ICU patients with candidemia[39,46,48,50,51]. Studies have shown that detection of mannan and anti-mannan antibodies offer a useful diagnostic aid in patients with invasive candidiasis than either test alone, particularly in hepato-oncologic patients where microbiological documentation of infection is more difficult[38,50]. Recently, newer versions of *Candida* mannan and anti-mannan antibody tests have been introduced (Platelia *Candida* Ag Plus and Platelia *Candida* Antibody Plus) with revised recommended cut-off values for a positive test and their performance in clinical studies is under evaluation. Although mannan and antimannan antibody tests have largely been used in Europe, they are not included in the revised EORTC/ MSG criteria for the diagnosis of invasive fungal *Candida* infections[25].

An indirect immunofluorescence assay has recently been developed by a Spanish group that detects antibodies against *C. albicans* germ tubes (CAGTA) and is also available commercially (*C. albicans* IFA IgG; Virvell Laboratories, Spain)[52]. The

Table 2: Performance of molecular assays for the diagnosis of candidemia and invasive candidiasis from selected studies

Molecular assay or format	Commercially available	DNA extraction procedure	*Candida* species detected	Sensitivity %	Specificity %
PCR	No	Manual	Major *Candida* species	95 - 100	98 - 100
Seminested / nested PCR	No	Manual	Major *Candida* species	100	98 - 100
Multiplex PCR	No	Manual	Major *Candida* species	75	97
Real-time PCR	No	Manual	Major *Candida* species	91 - 100	97 - 100
LightCycler SeptiFast	Yes	Automated	Five *Candida* species	90	97
MolYsis	Yes	Automated	Major *Candida* species	88	95

*Cumulative values for sensitivity and specificity are based on several published studies

overall sensitivity and specificity of CAGTA have been reported to vary from 77 - 89% and 91 - 100%, respectively, for the diagnosis of invasive candidiasis among different patient populations (intravenous drug abusers, transplant recipients, and hematologic or ICU patients)[52]. Although germ tube formation is limited to *C. albicans and C. dubliniensis*, the test was also positive in patients infected with other *Candida* spp. (*C. parapsilosis, C. glbrata, C. tropicalis, C. krusei and C. guilliermondii*) which is an unexplained observation. More studies are clearly needed to validate this assay for the diagnosis of invasive candidiasis in critical care settings.

NUCLEIC ACID AMPLIFICATION-BASED TESTS FOR DETECTION OF CANDIDEMIA AND INVASIVE CANDIDIASIS

The nucleic acid amplification techniques offer an attractive alternative to improve timely diagnosis of invasive candidiasis in high risk patients[53,54]. At present, different formats of both, in-house developed and commercial molecular tests are available for qualitative or quantitative detection of *Candida* species-specific DNA and many studies have yielded encouraging results. Commonly used platforms employed so far include conventional, semi-nested and nested PCR,[38,46,55-60], PCR-enzyme immunoassay[61-63], different variations of real-time PCR[58,64-68], multiplex PCR or multiplex PCR followed by DNA microarray[56,69], DNA sequencing and pyrosequencing (Table 2)[70-74]. Despite high potential of PCR-based tests, detection of nucleic acid in body fluids is challenging due to low pathogen burden and tough fungal cell walls which impede efficient lysis and liberation of DNA, leading to false-negative PCR results[53,68]. The presence of excessive amounts of human DNA and other PCR inhibitors may also lead to false-negative PCR results[53,68]. False-positive results also remain a major concern due to airborne-contamination of specimens, particularly if panfungal primers targeting highly conserved rRNA or other genes are used. Furthermore, as many *Candida* spp. are human colonizers of skin, mucosal surfaces or other anatomic sites, detection of target nucleic acids corresponding to few *Candida* cells in the clinical samples causes difficulty in distinguishing colonization from infection[53,75].

Quantitative real-time PCR assays are superior to other molecular methods as amplification of target DNA and detection are coupled in a closed environment which limits the risk of amplicon contamination and false-positive results[74]. Clinical evaluation studies of quantitative real-time PCR assays have reported sensitivities and specificities of > 90% for the detection of *Candida* species in serum samples from ICU patients (Table 2)[58,64-67,76]. Despite these advances, clinical applicability of PCR-based diagnosis of candidemia has been limited by optimal DNA extraction techniques, selection of optimal specimen type (whole blood or serum or plasma) and absence of a standardized and validated commercial test. More recently, automated DNA extraction procedures and standardized molecular technology platforms that meet accepted regulatory standards for clinical diagnosis have become available. The first commercially available real-time PCR method (LightCycler SeptiFast, Roche Diagnostics) designed to detect 25 most frequently isolated bloodstream microbial pathogens, including five *Candida* species, was introduced by Roche Diagnostics[77]. The test is performed directly on 1.5 ml of whole blood drawn at the same time as for blood culture. Extraction of both, human and pathogen DNA involves mechanical lysis and manual spin columns under a contamination-controlled workflow. The extracted DNA is amplified in three separate real-time PCR assays, one each for Gram-positive, Gram-negative and fungal pathogens. The amplicons are hybridized to species-specific fluorescent probes for identification of the pathogens and the test is completed in nearly six hours[77].

Initial evaluation of the LightCycler SeptiFast assay in ICU patients with hematological malignancies was promising as it exhibited 83% concordance with blood culture results and the discrepant results were in favor of SeptiFast as many samples from clinically suspected patients were PCR-positive but tested negative by culture. Subsequent evaluations employing larger and more diverse patient populations including neonates and children have yielded similar results (Table 2) [78-82]. The higher sensitivity of the LightCycler SeptiFast assay

is really not surprising since blood culture considered as the 'gold standard' of sepsis remains negative in ~ 50% of all clinical cases of sepsis including those caused by *Candida* spp.[83]. In some studies, the SeptiFast-positive, culture-negative cases were frequently recognized as clinically significant based on clinical data, disease severity and analytical evidence of infection and in some cases, were subsequently confirmed by positive culture of more appropriate clinical samples[83-85]. Other possible causes of LightCycler SeptiFast-positive, culture-negative cases could arise due to nonviable organisms in blood as a result of treatment, free circulating DNA released from remote infection sites or effect of prior antibiotic treatment on culture. However, some cases, particularly those caused by *C. glabrata* were detected more often by culture than by LightCycler SeptiFast, possibly due to low *Candida* count in bloodstream and smaller blood volume used for DNA extraction and subsequent analysis. Also, some LightCycler SeptiFast-negative, culture-positive or LightCycler SeptiFast-negative, culture-negative samples could be due to organisms that are not identified by the assay or unculturable organisms, respectively[83,84,86,87].

Another commercial test (MolYsis) employs a unique DNA extraction procedure that reduces the burden of human DNA, a major source of inhibition in PCR-based diagnostic methods. This is achieved by selective and gentle lysis of white blood cells to release human DNA and its removal by DNase treatment before lysis of fungal (and bacterial) cells is performed under more severe conditions to release pathogen nucleic acids from blood samples[88]. The extracted DNA is then amplified by a multiplex PCR and multiple amplicons are either sequenced or other detection formats are used to identify the pathogen in blood samples[89,90]. Since blood is used as clinical specimen for diagnosis, freely circulating pathogen DNA released into bloodstream from deep-seated infection sites is, however, also lost along with human DNA during initial stages of DNA extraction procedure and may cause false-negative results. A recent study detected nearly twice as many cases of infective endocarditis by MolYsis as compared to culture including mixed infections by bacterial and *Candida* species[91]. Another approach exploits methylation differences between human DNA and bacterial / fungal DNA for enrichment of pathogen DNA by affinity chromatography followed by 18S rRNA broad-range real-time PCR and was found to detect more candeidemia cases than culture[53,92]. These approaches hold great promise for sensitive detection of fungal bloodstream pathogens. A more extensive evaluation of the clinical utility of these approaches for invasive candidiasis is eagerly awaited.

RAPID IDENTIFICATION OF BLOOD CULTURE ISOLATES OF CANDIDA SPECIES

Identification of specific *Candida* species is also required even if blood cultures are positive for proper patient management which may take one to several days by conventional methods thus, delaying treatment with appropriate antifungal drugs. Both, phenotypic and molecular methods have been developed for rapid species-specific identification of blood culture isolates of yeast species in recent years. Phenotypic identification is time consuming and lacks specificity as it is based on analysis of the macro- and microscopic features of yeast colonies on solid culture (usually Sabourad dextrose agar), presence of pseudohyphae and chlamydoconidia, formation of germ tube in horse serum in 2-3 hours at 35º C (positive for *C. albicans* and *C. dubliniensis*), use of differential media (such as sunflower seed agar / tobacco agar for differentiation of *C. dubliniensis* from *C. albicans*) and evidence of assimilation or fermentation of sugars or other compounds by using automated / semiautomated systems such as Vitek 2 or ID32C yeast identification systems[31,54,93,94]. The use of chromogenic media (such as CHROMagar *Candida*) may be used to highlight mixed cultures during identification of yeast isolates[95].

Table 3: Molecular methods for rapid identification of clinical isolates of *Candida* species

Molecular method	Turn around time	*Candida* species identified	Main reference (s)
PCR-hybridization	2 days	CA, CP, CGl, CT, CL, CKr, CGu, CKe	60
Seminested PCR	1 day	CA, CP, CGl, CT, CL, CD, CKr, CGu, CR, CKe	57, 101, 103
PCR-microarray	1 day	All major pathogenic species	69, 111
Real-time PCR	1 day	CA, CGl, CP, CT, CKr	64, 65, 102
PCR-sequencing	1 - 2 days	All pathogenic species	70 - 72
PCR-pyrosequencing	1 - 2 days	All pathogenic species	73, 74
SeptiFast real-time PCR	4 - 6 hours	CA, CP, CGl, CT, CKr	77 - 83
MALDI-TOF MS	15 - 20 min	All major pathogenic species	115, 118-122
PCR/ESI-MS	4 - 6 hours	All major pathogenic species	124, 125

CA = *Candida albicans*; CP = *Candida parapsilosis*; CGl = *Candida glabrata*; CT = *Candida tropicalis*; CL = *Candida lusitaniae*; CD = *Candida dubliniensis*; CKr = *Candida krusei*; CGu = *Candida guilliermondii*; CR = *Candida rugosa*; CKe = *Candida kefyr*

However, application of phenotypic methods is time consuming and may take one to several days for species-specific identification.

Molecular methods offer rapid species-specific identification of blood culture isolates[31,53,54]. Conventional PCR with panfungal primers followed by species-specific detection of amplicons (using probe primers) by enzyme immunoassay or uniplex / multiplex PCR with species-specific primers followed by gel electrophoresis is normally carried out for identification of most frequently isolated *Candida* species (Table 3)[28,57,59-63,96-101]. Panfungal real-time PCR assays using species-specific probe primers in a closed system that is less prone to cross contamination yield faster results in a single step. However, practical application of using distinct probe primers in a single reaction is limited[64,102]. Panfungal PCR followed by sequencing (or pyrosequencing) of species-specific regions of *Candida* DNA or hybridization with specific probe primers on a microarray is suitable for rapid detection of both, frequent as well as rare agents of candidemia and invasive candidiasis (Table 3)[7,28,29,70-74,103-110]. Similarly, PCR amplification followed by hybridization with specific probe primers on a microarray[69,111] or hybridization to specific capture probes bound to microbeads by Luminex technology[112,113] is also suitable for rapid detection of a wide array of pathogenic *Candida* species cultured from a variety of clinical specimens.

A novel method exploited recently for reliable and rapid identification of *Candida* spp. isolates is Matrix-Assisted Laser Desorption / Ionization-Time of Flight Mass Spectrometry (MALDI-TOF MS)[114,115]. The method employs ionization of large and delicate cell surface macromolecules such as proteins without extensive degradation into the gas phase for acceleration across an electric field within the ionization chamber to a velocity that depends on the mass-to-charge ratio. The particles then enter the TOF mass analyzer for determination of the mass spectrum. The technique generates protein fingerprints of microorganisms and the identity is established by comparing to reference spectra of a well-characterized library of organisms)[116,117]. The method has been evaluated extensively in several recent studies for the identification of *Candida* and other pathogenic yeast species cultured on a variety of selective fungal isolation media, including Sabouraud's agar (SDA), Mycosel agar, inhibitory mold agar (IMA), yeast extract peptone dextrose (YEPD) agar and blood culture broth)[114,115,116-123]. Even closely related *Candida* species and species complexes such as *C. albicans* and *C. dubliniensis, C. parapsilosis, C. orthopsilosis* and *C. metapsilosis* and *C. glabrata* and *C. bracarensis* can be easily identified by MALDI-TOF MS within 15 - 20 min (Table 3)[122,123]. The sensitivity of > 90% has been reported for species-specific identification of cultured isolates of yeast and *Candida* species)[118,121,122]. Although blood cultures have also been used directly, a minority of samples may fail analysis due to presence of mixed cultures (bacterial and fungal or two different yeast species) as mixed cultures may influence the spectral quality during MALDI-TOF MS analysis[122,123].

Another strategy that has been developed recently for detection and identification of bloodstream pathogens employs broad-range PCR amplification of highly conserved gene regions (such as 18S, 5.8S or 28S rRNA genes for fungal pathogens) that encompass species-specific sequences (internal transcribed spacer 1 and 2 sequences) or other housekeeping genes followed by precise determination of the mass and thereby base composition of amplicons by electrospray ionization / mass spectrometry (PCR / ESI-MS)[53]. Panfungal (or pan*Candida*) primers are used and no probes are required, hence any culturable (or non-culturable) *Candida* spp. can be detected and identified in clinical samples. The method involves amplification of several gene loci followed by fully automated electrospray ionization / mass spectrometry (ESI-MS) analysis of amplicons on PCR / ESI-MS instrument. The molecular mass of amplicon or mixture of amplicons is accurately obtained and base composition of A, G, C and T is deduced for each amplicon, the latter is then compared with signature reference standards (base compositions of amplicons of known organisms previously determined with PCR / ESI-MS) for identification. Three primers pairs targeting rDNA and one primer pair targeting mitochondrial 18S rRNA have been used for detection and identification of eight medically important *Candida* spp. including *C. albicans*, *C. dubliniensis, C. parapsilosis, C. glabrata, C. tropicalis, C. lusitaniae, C. guilliermondii* and *C. krusei*[53]. In case, there is no perfect match with a sequence in the database, the nearest neighbor organism is identified, an approach similar to the nucleotide sequence-based identification by BLAST. Although the method has not been evaluated extensively, few studies have reported excellent concordance between PCR / ESI-MS and repetitive sequence PCR for well-characterized reference strains of several *Candida* spp. of clinical relevance and clinical isolates of *Candida* spp[124,125].

CONCLUSIONS

The absence of specific signs and symptoms and low blood culture positivity even in proven cases of invasive candidiasis has always posed a diagnostic challenge to clinicians and microbiologists alike. However, sustained efforts by investigators in recent years have led to the development of new antigen and molecular / DNA-based approaches which have proved useful adjuncts to the early diagnosis of candidemia / invasive candidiasis and species-specific identification

of *Candida* species. Two antigen-based tests, β-D-glucan, a panfungal marker and *Candida* mannan, a genus-specific marker are now commercially available and have been evaluated with variable sensitivities and specificities. Due to high negative predictive value of these tests, serial monitoring of biomarkers in select category of high-risk patients, allows clinicians to withhold antifungal agents as long as they remain negative and to use them preemptively to prevent full blown disease when they turn positive. Concomitant detection of two or more circulating biomarkers improves sensitivity and / or specificity. Significant progress has also been made in developing nucleic acid-based tests. A commercial, real-time PCR-based test (Septi-Fast) can detect five most frequently isolated *Candida* spp. in blood specimens from suspected patients within six hours. Novel technologies such as high throughput sequencing and MALDI-TOF MS have also been developed recently to reduce the time required for species-specific identification of clinical yeast isolates. The authors hope that this review will create a greater awareness among the clinicians about the usefulness of biomarkers in the diagnosis of invasive candidiasis. An integrated approach based on clinical judgment, risk factors, and biomarkers levels will help clinicians to make a timely decision about initiation of pre-emptive therapy before a full-blown disease develops.

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Original Article

Varicella-Zoster Infection in Adult Males: Risk Factors for Varicella-Zoster Virus Pneumonia

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ABSTRACT

Objectives: To study the risk factors for varicella pneumonia (VP) in adults and to predict the early progression to severe pneumonitis in order to establish early therapeutic intervention
Design: Prospective study
Setting: Infectious Diseases Hospital
Subjects and Methods: Fifty-two male patients with VP and 52 Varicella patients without pneumonia as control. Beside history taking and routine work-up, all cases were subjected to arterial blood gas analysis, and hypoxemic index (HI) was calculated as an indicator for severity of pneumonia
Interventions: Arterial blood gas analysis
Main Outcome Measures: Occurrence of VP
Results: Univariate analysis revealed significant associations between pulmonary findings, chronic diseases, severe varicella rash and smoking in patients with VP than those without pneumonia ($p = 0.001, 0.03, 0.001, 0.03$ respectively). Blood gas analysis showed significantly lower mean values of PaO_2, SaO_2 and hypoxemic index in patients with VP than controls ($p = 0.001$). However, the mean $PaCO_2$ was significantly higher in the same patient group ($p = 0.001$). Multivariate analysis demonstrated that older age, clinical pulmonary findings, severe varicella rash, low PaO_2, low HI and FDPs > 1000 were significantly associated with VP.
Conclusion: In adult males with VP, presence of HI < 150, generalized radiological pulmonary opacities, FDPs > 1000, low PaO_2 and SaO2% could be considered good predictors of progression to serve VP. These factors should alert the physician for an early intervention as VP is potentially life-threatening.

KEY WORDS: chickenpox, hypoxemic index, pneumonia, varicella

INTRODUCTION

Varicella-Zoster is a DNA herpes virus, and infection occurs primarily as varicella (chickenpox) or herpes zoster (shingles)[1]. Varicella is a common childhood illness causing a mild febrile illness with a characteristic rash[2].

In healthy children, the course of a varicella infection is typically benign. However, in adults and immune-compromised children it can be complicated by pneumonic, hematologic, and neurologic manifestations, of which pneumonia is the most common[3].

It was reported that the absolute number and proportion of varicella-zoster infections occurring in adults has been rising over the past 20 years[4]. The reason for this is ill-understood and may include smaller family size, less exposure to varicella-zoster virus during childhood and increased virulence of the virus[5].

Several risk factors exist that can give the clinician a clue for lung involvement in the adult patient with varicella infection. Immunosuppression, chronic obstructive pulmonary disease (COPD), old age, smoking, pregnancy, and a severe cutaneous or hemorrhagic rash increase the occurrence of pneumonia[3,6]. Despite the increasing frequency, little data exists on the prognosis of adult patients with varicella pneumonia (VP). The purpose of this study was to look for the occurrence of VP among adult male patients with chickenpox who were admitted to infectious diseases hospital (IDH), Kuwait, to reiterate the risk factors for the development of VP and to predict the early progression to severe pneumonitis in order to establish early therapeutic intervention.

SUBJECTS AND METHODS

Subjects

This prospective study enrolled 52 adult male patients with chickenpox and VP who were admitted to the IDH over a four year period from August 2007 to July 2011. Inclusion criteria entailed a classic chickenpox rash in a patient with pulmonary infiltrates

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on the chest radiograph. Thus, all the patients were enrolled in the study after the diagnosis of VP had been made. In addition, an equal number of adult males with chickenpox not associated with pneumonia were enrolled as controls.

IDH is the referral center for all infectious diseases in Kuwait.

Methods

All patients with VP and control group were admitted and managed in the IDH, Kuwait. They were subjected to the following:

1. Thorough history taking with respect to patient demographics, history of contact with varicella, any previous pulmonary disease, chronic illness, and immunosuppressive states or any other risk factor
2. Complete physical examination
3. Hematologic investigations: complete blood picture and coagulation profile
4. Complete biochemical investigations including renal profile, hepatic profile and serum electrolytes
5. Assessment of arterial blood gases: arterial blood samples were taken at the time of diagnosis and during therapy by the use of Roche Micro-sampler (Roche Diagnostics Corporation). To obtain true results of the arterial blood gases, the first arterial blood sample was collected while the patient was not on oxygen inhalation.
6. Monitoring of oxygen saturation by means of a pulse oximeter 504 (Criticare System Inc.)
7. Hypoxemic index (HI): This was used as an indicator of the severity of the pneumonia. It was calculated as the partial pressure of arterial oxygen in (mmHg) divided by the fractional inspired oxygen tension[7]. Severe pneumonitis was defined as a HI of less than 150.

Statistical analysis

Data were collected and coded then entered into an IBM compatible computer, using the SPSS version 12 for Windows. Qualitative variables were expressed as number and percentage while quantitative variables were expressed as mean ($\bar{\chi}$) and standard deviation (S). The arithmetic mean ($\bar{\chi}$) was used as a measure of central tendency, while the standard deviation (S) was used as a measure of dispersion. For quantitative variables, t-test was used to compare between two means, while, for qualitative variables, chi-square ($\chi 2$) test, likelihood ratio (LLR), or Fisher's exact test were used when appropriate. The relationship between predisposing factors and the occurrence of VP was expressed in terms of odds ratio (OR) together with 95% confidence intervals (95% CIs).

RESULTS

Fifty two adult patients with VP were selected from varicella patients who were admitted to IDH. All selected patients were male with a mean age of 36.85 ± 7.24 years and a range of 20 - 52 years. The control group included 52 male patients with uncomplicated varicella and their ages ranged between 19 and 41 years, with a mean of 30.38 ± 6.6 years. The mean age of patients with VP was significantly higher than the mean age of the control group (Table 1). Patients with VP were of different nationalities. There were 15 Arabs (28.85%), and 37 non-Arabs (71.15%). Amongst the Arab patients there were 11 Kuwaiti, three Saudi, and one Egyptian, while amongst the non-Arabs there were 18 Indians, 10 Bangladeshi, four Srilankan, and five Philippino men. Statistical analysis revealed no significant difference between nationalities of patients and those of the control group (Table 1).

Table 1: Some demographic and clinical data

Patient data	VP N = 52	V without P N = 52	Significance p- value
Age in years mean ±SD	36.85 ± 7.24	30.38 ± 6.6	0.001*
Nationality			
Arab n (%)	15 (28.85)	7 (13.46)	0.055
Non-Arab n (%)	37 (71.15)	45 (86.54)	
Symptoms			
CS (fever & rash) n(%)	31 (25)	43 (82.69)	0.001*
CS + additional symptoms n (%)	39 (75)	9 (17.31)	
Associated chronic disease n (%)	12 (23.07)	4 (7.7)	0.03*
Smoking n (%)	24 (46.15)	10 (19.23)	0.003*

* = significant at $p < 0.05$; VP = Varicella Pneumonia; n = number, SD = standard deviation, CS: classic symptoms

Symptoms of fever and chickenpox rash were present in all cases of varicella with and without pneumonia. However, additional symptoms of cough and breathing difficulty were significantly evident in VP cases than the control group (75% & 17.31% respectively) (Table 1). Contact history showed that 45% of all the study cases had contracted varicella from their children, 24% from their house contacts, 3% from their partners, while contact history was not identified in 28% of cases.

Out of the 52 patients with VP, 12 patients (23.07%) had an associated chronic disease. Eight of them (15.4%) had chronic lung disease (COPD, asthma, previous pneumonia or tuberculosis), one patient had neuropsychiatric problems, one was diabetic, one had chronic myeloid leukemia on treatment, and one had chronic alcoholism. On the other hand four patients

(7.7%) in the control group had diabetes mellitus. No one was receiving immunosuppressive drugs, but one patient with leukemia was taking an alkylating agent (Busulfan) 2 mg orally per day as maintenance therapy. Statistical analysis showed a significant association of chronic diseases in patients with VP than those without pneumonia (p = 0.03 S*) (Table 1).

Smoking was positive in 24 patients with VP (46.15%), and in nine patients from the control group (17.31%). Univariate analysis showed that there was a significantly higher proportion of smokers among those with VP (p = 0.003) (Table 1).

Table 2 shows the main clinical findings. Severe skin rash was encountered in significantly higher number of patients with VP than those without VP (LLR = 32.547, p = 0.001S*). Mucosal affection by varicella rash was similarly more associated in patients with VP than controls (p = 0.002 S*). Moreover, presence of abnormal physical lung signs such as wheezes, rales, and abnormal breath sound was reported in 47 patients with VP in contrast to absence of such findings in the control group (p = 0.001*).

Regarding the chest X-ray findings, all patients with VP had been enrolled in the study due to positive lung X-ray findings. 19 patients (36.54%) had generalized pulmonary opacities (Fig. 1), and 33 patients (63.46%) had focal and or linear opacities (Fig. 2). On the contrary, all patients without pneumonia had normal X-ray chest (Table 2).

Table 2: Main clinical findings

Findings	VP N = 52 n (%)	V without P N = 52 n (%)	Significance
Skin rash			LLr = 32.547
Non-severe	9 (17.30)	37 (71.15)	0.001*
Severe	43 (82.69)	15 (28.85)	
Affected mucosa	41 (78.85)	26 (50)	X^2 = 9.439 0.002*
Chest findings	5 (9.62)	52 (100)	FET
No chest signs	47 (90.38)	0 (0.00)	0.001*
Positive chest signs			
X-Ray chest	19 (36.54)	0 (0.00)	
Generalized opacity	33 (63.46)	0 (0.00)	
Focal opacity			

V = varicella, P = pneumonia, *= significant at p < 0.05, LLR = likelihood ratio, x^2 = Chi square test, FET= fisher's exact test

Table 3 shows the hematological findings in both the groups. Statistical analysis revealed a significantly lower platelet counts in VP group than control (p = 0.001). In contrast, total leucocytic count, prothrombin time and activated partial thromboplastin time showed significantly higher mean values in patients with VP than the controls. However, all the values were within normal range.

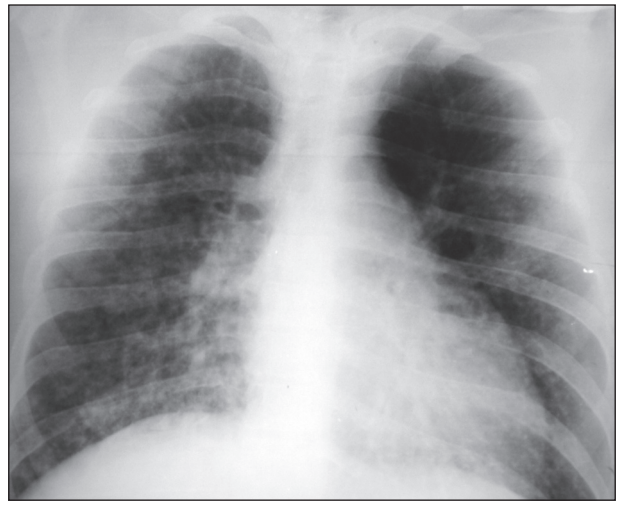

Fig. 1: Chest radiograph of Varicella pneumonia showing generalized pulmonary opacities

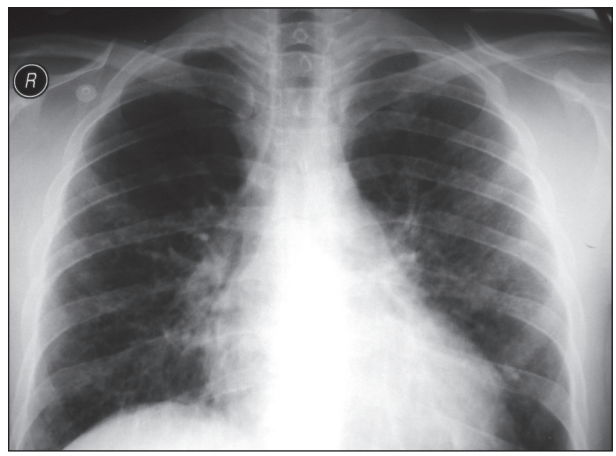

Fig. 2: Chest radiograph of Varicella pneumonia showing linear and focal pulmonary opacities

Table 3: Hematological laboratory investigations

Laboratary investigation	VP N=52		Vwithout P N = 52		t-test	p-value
	Mean	SD	Mean	SD		
Total WBC ($x10^9$/l)	7.96	2.87	6.64	2.24	2.612	0.010 *
Total RBC ($x10^{12}$/l)	5.28	0.49	5.06	0.57	2.090	0.039
Hb (g/l)	151.05	30.57	150.21	7.20	0.192	0.848
Platelets ($x10^9$/l)	142.67	44.06	209.42	59.17	6.524	0.001 *
ESR(mm/h)	24.98	4.50	19.19	14.89	2.684	0.008
PT (sec)	13.27	0.85	12.05	0.98	6.821	0.001 *
INR	1.29	0.15	1.27	0.11	0.764	0.447
APTT(sec)	34.69	4.71	32.65	1.31	3.009	0.003 *

V= Varicella, P= pneumonia, WBC = white blood cells, l = liter, RBC = red blood cells, Hb = hemoglobin, g = gram, ESR = erythrocyte sedimentation rate, PT = prothrombin time, INR = international normalized ratio, APTT = activated thromboplastin time, SD = standard deviation. * = significant at p < 0.05

On admission, the biochemical laboratory findings (Table 4), revealed that serum alanine transpeptidase (ALT), aspartate transpeptidase (AST), and lactate dehydrogenase (LD) were significantly higher in patients with VP than in the control group. On discharge, such findings reverted to normal or near normal levels.

Table 4: Some biochemical laboratory investigations

Laboratary investigation	VP N = 52		V without P N = 52		t-test	p-value
	Mean	SD	Mean	SD		
Glucose (mmol/l)	7.12	1.80	6.77	1.53	1.057	0.293
Creatinine (umol/l)	103.69	21.53	98.98	8.17	1.475	0.143
Total bil (umol/l)	12.97	3.26	13.93	1.97	1.800	0.075
ALB (g/l)	37.44	6.96	37.08	2.49	0.353	0.725
ALT (IU/l)	93.08	57.67	50.02	8.56	5.325	0.001*
AST (IU/l)	85.87	50.72	35.42	10.03	7.035	0.001*
ALP (IU/l)	83.27	20.01	81.46	13.17	0.544	0.587
LD (IU/l)	454.38	268.79	171.33	28.09	7.553	0.001*

V = varicella, P = pneumonia, Total bil = total bilirubin, ALB = albumin, ALT = alanine transpeptidase, AST = aspartate transpeptidase, ALP = alkaline phosphatase, LD = lactic dehydrogenase, SD = standard deviation, mmol/l = millimol/liter, umol/l = micromol/liter, IU/l = international unit/liter. * = significant at p <0.05

Results of arterial blood gases were studied in all varicella patients with and without pneumonia. Statistical analysis demonstrated a significantly lower mean value of arterial oxygen tension (PaO_2) in patients with VP than controls (p = 0.001). Meanwhile, the mean arterial carbon dioxide tension ($PaCO_2$) was significantly higher in patients with VP (p = 0.001). The mean arterial oxygen saturation (SaO_2) was significantly lower in VP cases than controls (p = 0.001). Furthermore, the mean value of hypoxemic index (HI) was significantly lower in patients with VP (p = 0.001, Table 5). According to the value of HI, patients with VP were categorized as severe VP if the HI < 150 and non-severe pneumonia if the HI > 150 (Table 6).

Table 5: Main findings of arterial blood gases and hypoxemic index

Blood gas and index	VP N = 52		Vwithout P N = 52		t-test	p-value
	Mean	SD	Mean	SD		
PaO_2 (kPa)	7.45	1.76	11.43	1.99	10.801	0.001*
$PaCO_2$(kPa)	4.58	0.65	3.84	0.21	7.841	0.001*
PH	7.38	0.06	7.40	0.00	1.806	0.074
BE	-3.06	2.45	-3.50	0.69	1.232	0.221
$CHCO_3$	21.18	2.30	22.37	0.52	3.642	0.001*
SaO_2 %	91.31	7.57	97.85	1.26	6.150	0.001*
HI	236.40	90.75	426.02	97.96	10.240	0.001*

V = varicella, P = pneumonia, PaO_2 = arterial oxygen tension, kPa = kilopascal, $PaCO_2$ = arterial carbon dioxide tension, BE = base excess, $CHCO_3$ = bicarbonate, SaO_2% = arterial oxygen saturation, HI = hypoxemic index. * = significant at p < 0.05

Table 6: Comparison of severe and non-severe cases of VP (severity defined as a HI < 150)

Factors	Severe pneumonia N = 14 n (%)	Non-severe pneumonia N = 38 n (%)	Significance
Mean age (years)	34.79	37.61	0.216 NS
Arabs	7 (50)	8 (21.05)	0.081 NS
Non-Arabs	7 (50)	30(78.95)	
Smoking	8 (57.14)	16(42.11)	0.335 NS
CS	21.43	26.32	1.000 NS
CS+PS	78.57	73.68	
Associated CD	5 (35.71)	7 (18.42)	0.189 NS
Severe SR	12 (85.71)	31 (81.58)	0.718 NS
Positive chest signs	13 (92.86)	34 (89.47)	1.000 NS
Generalized CXR			0.001*
opacities	12 (85.71)	7 (18.42)	0.001*
FDPs > 1000	9 (64.29)	2 (5.26)	
Mean PaO_2	5.65	8.11	0.001*
Mean %SaO_2	85.76	93.35	0.001*
Patients need ICU	12 (85.71)	1 (2.63)	0.001*

NS = not significant, CD: chronic disease, CS = classic symptoms, PS = pulmonary symptoms, SR = skin rash, CXR = chest X-ray, FDPs: fibrinogen degradation products, ICU = intensive care unit, NS = not significant

There was no significant difference between patients with severe and non-severe VP in terms of age, nationality, smoking, presenting symptoms, associated chronic diseases, skin rash and chest physical signs (Table 6). However, in the univariate analysis, all these factors except nationality were significantly found to be associated in patients with VP when compared with the control group (Tables 1 & 2). The risk of progression to severe pneumonia was significantly increased in patients with HI < 150, with generalized opacities in the chest X-ray, in those with serum level of fibrinogen degradation products (FDPs) > 1000, and in those with lower values of PaO2 and SaO2% (Table 6). Moreover, 12 out of 14 patients with severe pneumonia (85.71%) required intensive care management as compared to only one patient (2.63%) out of 38 patients who had non-severe pneumonia (Table 6).

Factors associated with VP were used in a multivariable logistic regression analysis (LRA) to evaluate further the relationship between these factors and VP (Table 7). Although these factors were significant in VP cases on univariate analysis, (Tables 1, 2 & 5), not all of them showed significant odds ratios when multivariable LRA was applied (Table 7).

Table 7: Factors associated with Varicella pneumonia and multivariable logistic regression analysis

Factors	Pneumonia N = 52 %	No pneumonia N = 52 %	Odds ratio	95% CI
Mean age (yrs)	36.85	30.38	1.16*	1.05 - 1.28
Pulmonary symptoms	75	17.31	10.479*	2.74 - 40.15
Severe rash	82.69	28.85	6.23*	1.96 -19.83
Smoking	46.15	19.23	0.828	0.22 - 3.13
Chronic disease	23.07	7.7	0.369	0.06 - 2.24
Positive pulmonary signs	90.38	0.00	2.38*	2.7 - 7.81
Mean platelet	142.67	209.42	0.62	0.8 - 2.56
Mean PaO2 (kPa)	7.45	11.43	3.04*	1.6 - 10.9
Mean HI	236.4	426.02	4.21*	3.21 - 4.17
FDPs >1000	11 (21.15)	0 (0.00)	1.94*	1.4 - 2.63

CI= Confidence Interval

After diagnosis, all patients with VP were immediately started on acyclovir 10 mg/kg every eight hours, in addition to other supportive measures. Thirty-eight patients (73.08%) were cured without need to intensive care measures. One patient (1.92%) died a short time after admission. Thirteen patients (25%) were admitted to the intensive care unit (ICU) due to acute hypoxemic respiratory failure. Three patients received non-invasive positive pressure ventilation *via* a face mask and the other ten patients with the clinical diagnosis of acute respiratory distress syndrome (ARDS) were intubated and mechanically ventilated. Two patients died in the ICU due to multiple organ failure, while, the remaining 11 patients recovered completely. Consequently, statistical analysis revealed that the average hospital stay was significantly more in patients with VP than those without (10.19 ± 4.62 days and 5.19 ± 0.72 days respectively, p= 0.001).

DISCUSSION

Varicella is highly contagious. Epidemiological data suggests that the incidence of primary varicella infection in adults is increasing[4]. Such infection in adults is more frequently associated with complications[8], of which pneumonitis is the most common. All our cases had the symptoms of fever and varicella rash, while additional respiratory symptoms including cough and shortness of breath were present in 75% of cases with VP. This is in agreement with the previous study which reported that the presence of respiratory symptoms was an excellent indicator of pneumonitis[1]. In contrast, there were two reported cases of VP which developed in the absence of any respiratory symptoms[9]. Hemoptysis, was reported by some authors as a common finding[9], but it was not observed in any of our VP patients. Multivariable LRA done on our cases showed that patients with respiratory symptoms were ten times at greater risk of developing VP as controls (odds ratio 10.479*).

In the univariate analysis, smoking was statistically significant in cases of VP than those without pneumonia. This finding was similar to an earlier report in which the univariate analysis revealed that smoking was a significant factor in adult patients with primary varicella[10]. A recent retrospective study done on 21 men and 25 women showed that 35 (76%) of them were active smokers[11]. Another study reported that 77.3% of their VP patients were smokers by using the same statistical tests[12]. However, in our multivariate analysis, smoking was not associated with a significant odds ratio in contrast to the previous study which showed that smoking was associated with an increased incidence of VP but it was in pregnant women[13]. Yet another study stated that VP was associated with current smoking among 19 patients with male to female ratio of 12:7[2]. Therefore, further studies including male and female patients and a larger sample size to confirm such results are required.

It was thought that smoking may predispose to VP as a result of the direct effect of cigarette smoke on the pulmonary macrophages making them more susceptible to infection by herpes viruses[14].

Moreover, varicella patients with chronic pulmonary diseases such as COPD and asthma were more liable to develop pneumonia in the univariable analysis (Table 1). However, on applying the multivariable LRA, such patients seemed to have 30% higher risk of developing pneumonia as compared to the control.

In agreement with our study, some other authors also have stated that a higher number of varicella skin lesions are associated with greater frequency of VP[12,15], but the findings of an Australian study did not support that conclusion[16]. LRA showed that the risk of developing VP was six times greater in patients with severe skin rash than those with non-severe rash (odds ratio 6.23, CI 1.96 - 19.83*S).

The presence of a HI < 150, the generalized chest X-ray findings of pneumonia, fibrinogen degradation products (FDPs) > 1000, low arterial oxygen tension (PaO_2) and low arterial oxygen saturation (SaO_2%) were statistically significant indicators for progression to severe pneumonia in our study. However, applying the multivariable LRA on our cases, those who had pulmonary symptoms, severe skin rash, low mean PaO2, low HI and older age group were at a significant greater risk of developing pneumonia. These findings are largely consistent with the results of previous studies[3,12,13,17].

Based on our results of the univariable and multivariable LRA, we may conclude that in any adult male patient with varicella, the presence of respiratory symptoms, severe varicella rash, smoking, low PaO_2, low HI and older age are significant factors leading to the development of VP. Moreover, in adult males with VP, presence of HI < 150, generalized radiological pulmonary opacities, FDPs > 1000, low PaO_2 and SaO_2% could be considered good predictors of progression to severe pneumonia. This should alert the physicians for an early intensive management, since early treatment of VP is potentially life-saving.

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Original Article

Early and Late Ovarian Hyperstimulation Syndrome: Two Distinct Clinical Entities

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ABSTRACT

Objectives: To study the differences in clinical characteristics of early and late ovarian hyperstimulation syndrome (OHSS) and its association with the occurrence of pregnancy and early pregnancy outcome
Design: Prospective study
Setting: Department of Obstetrics and Gynecology, Institute of Kidney Diseases and Research Center, Ahmedabad, India
Subjects: Thirty patients who developed OHSS out of 324 IVF / ICSI cycles over a one-year period
Intervention: All patients developing OHSS were hospitalized and managed conservatively.
Main Outcome Measures: Incidence of OHSS at our center, OHSS and pregnancy outcome and their course in the hospital
Results: Early OHSS occurred in 18 patients and late OHSS complicated 12 patients, the overall incidence being 7.7%. Early OHSS patients as compared to late OHSS group were characterized by significantly higher serum estradiol (E2) levels and the number of follicles on the day of hCG administration, and the number of oocytes retrieved. Clinical pregnancy occurred in all cycles with late OHSS. No significant difference was observed in occurrence of multiple pregnancy between the two groups. Late OHSS cases were more severe than early cases.
Conclusion: Serum E2 levels, the number of follicles on the day of hCG administration, and the number of oocytes retrieved can be used to predict the occurrence of early OHSS.

KEY WORDS: E2, multiple pregnancy OHSS,pregnancy outcome

INTRODUCTION

Ovarian hyperstimulation syndrome (OHSS) is an iatrogenic complication in 5 - 10% of all controlled ovarian hyperstimulations for assisted reproductive technology[1]. It is a potentially life-threatening condition in its severe form, resulting in hospitalization in 1.9% of cases and is characterized by marked multiple follicular enlargement, intravascular volume depletion, and hemoconcentration[2].

There are various risk factors associated with the development of OHSS, including polycystic ovaries, young age, previous OHSS, higher dose of exogenous gonadotropins and the administration or production (pregnancy) of hCG[3]. The exact pathogenesis of OHSS is complex and its etiology is still unclear. However, it has been recognized that hCG, either exogenous or endogenous *via* the production of the angiogenic molecule vascular endothelial growth factor (VEGF) plays a role in triggering this syndrome[4].

The dominant features of OHSS are increased capillary permeability, arteriolar vasodilatation, and variable ovarian enlargement.The increased capillary permeability causes a fluid shift from the blood stream, which in turn causes dehydration and thus hemoconcentration. The degree of fluid shift dictates the amount of hemoconcentration and the amount of extravascular fluid and thus the severity of the syndrome[5].

Classification of OHSS

Two main clinical forms of OHSS, early and late OHSS, distinguished by their time of onset, are described in the literature. Early OHSS is correlated to ovarian response to stimulation and is an acute effect of exogenous hCG administration, usually occurring within nine days after oocyte retrieval[6,7]. In contrast, late OHSS occurs after the initial 10-day period and is only poorly correlated to the ovarian response and is

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rather more correlated to the endogenous hCG produced by an implanting embryo or to the administration of hCG for luteal phase support (LPS)[7,8].

Conventionally severity of OHSS has been staged depending upon the clinical symptoms and laboratory findings. The first classification was proposed by Rabau[9] *et al* in 1967, and was later modified by Schenker and Weinstein[10]. It included three categories of mild, moderate, and severe, as well as six grades of severity. Golan[11] *et al* modified the classification, using only five grades, although some argued the severe category warranted further distinction. Navot *et al*[3] further contributed to the classification, based on clinical criteria and by reviewing and comparing risk factors and previous treatment strategies.

There are only a few previous studies comparing clinical consequences in early and late OHSS[6-8], and some conclusions are still contradictory. This study was performed to distinguish the characteristics of ART cycles complicated by early and late OHSS.

SUBJECTS AND METHODS

This prospective observational study was conducted in the Department of Obstetrics and Gynecology at Institute of Kidney Diseases and Research Center (IKDRC), Ahmedabad, India. It was approved by ethical committee of the institute. Between January 2011 and December 2011, a total of 324 IVF or ICSI cycles were performed in our center. Thirty women developing OHSS during that period were enrolled in the study. Informed consent was taken from all the participants.

OHSS was classified as the late type, if it occurred 10 or more days after oocyte retrieval, and early type, if it occurred within nine days[3]. The onset of OHSS was defined as the day of admission because of uncertainty of the exact onset of symptoms.

The criteria by Golan *et al*[11] were used to assess the severity of OHSS. Moderate OHSS is characterized by abdominal distension and discomfort, nausea, vomiting or diarrhea, enlarged ovarian size (5 - 12 cm), and ultrasonographic evidence of ascites. Severe OHSS is characterized by variable ovarian enlargement, massive ascites ± hydrothorax, hematocrit > 45% and white blood cell > 15,000/ml. Critical OHSS, initially suggested by Navot *et al*[5], was characterized by variable ovarian enlargement, tense ascites, hydrothorax, hematocrit > 55%, white blood cell count > 25,000/ml, oliguria, creatinine > 1.6 mg/dl, creatinine clearance < 50 ml/min, renal failure, thromboembolic phenomena, and acute respiratory distress syndrome (ARDS).

Although there has been no clear definition about massive ascites in severe OHSS, ascites that needed paracentesis due to clinical symptoms were considered as massive form. All patients developing OHSS were hospitalized and treated conservatively until there was spontaneous resolution of symptoms and improvement of clinical and laboratory findings. In-patient management was followed as suggested in the current literature[3,12,13,14]. Antiemetics and analgesics were prescribed for symptomatic relief. In moderate and severe OHSS cases, daily monitoring of input-output, abdominal girth and body weight was done. Laboratory determination of hematocrit, leukocyte count, electrolytes, serum creatinine, C-reactive protein (to exclude concomitant infection), coagulation profile and D-dimers was done on a daily basis. Volume replacement (if needed) was started with intravenous normal saline solution. Albumin (200 ml of 25% albumin solution over 4 h), was infused only in cases of severe OHSS. Paracentesis was performed when the patient had respiratory distress and severe abdominal distension and discomfort.

Stimulation Protocol

Stimulation protocol was selected according to the patient's characteristics and clinician's experience. For the GnRH agonist long protocol, patients received daily injection of 0.5 mg of leuprolide acetate starting on day 21 of the previous cycle. After confirmation of pituitary down-regulation, gonadotropin injections were initiated on cycle day 2. The initial gonadotropin dose remained fixed for the first 4 or 5 days, followed by adjustment on the basis of individual follicular growth and E2 levels until the day of hCG administration[8,15].

According to GnRH agonist short protocol, the GnRH agonist administration was initiated on day 2 of the cycle followed by gonadotropin injections on day 3 until hCG administration. In accordance with the GnRH antagonist protocol, gonadotropin was started on cycle day 2 or 3. The initial gonadotropin dose remained fixed for the first 4 or 5 days and when the leading follicle reached a diameter of 14 mm, cetrorelix 0.25 mg was added daily until the day of hCG administration[8,15].

In all the protocols, follicular growth was monitored by transvaginal ultrasound (TVS). Serum E2 levels were measured on day 4 or 5 of the stimulation and repeated as appropriate. The ovulation triggering dose of hCG, 10,000 IU was administered subcutaneously when the criterion of the presence of at least three follicles of 18 mm was reached. Oocytes were inseminated within four hours of retrieval either by conventional IVF or by ICSI. Embryos were transferred into the uterine cavity on days 2 or 3 (cleavage stage) or day 5 (blastocyst stage) after fertilization.

Luteal support was provided with vaginally administered progesterone suppositories (cyclogest) at a dosage of 600 mg daily in three equal doses beginning the day after ovulation triggering. A clinical pregnancy was defined as the presence of gestational sac (s) with pulsating fetal heart beats 3 - 4 weeks

after oocyte retrieval. Pregnancy losses before this period were described as preclinical miscarriage. A clinical miscarriage was defined as an abortion after identifying gestational sac (s) and up to 20 weeks of gestation. An ongoing pregnancy was defined, if a pregnancy continued beyond 12 weeks of gestation.

Statistical analysis

Statistical analysis was performed using the program, Statistical Package for the Social Sciences (SPSS version 12.0). Continuous variables were compared using independent two sample t- test and also Mann Whitney U-test. Chi square test or Fisher exact test were used to assess the effect of change in differences in categorical variables. Data values are expressed as mean ± SD, count (% and age) and $p < 0.05$ was considered to be statistically significant.

RESULTS

Overall, 324 IVF–ICSI cycles were performed during the study period, and OHSS occurred in 30 patients (7.7%). Early OHSS presented in 18 patients, whereas the late type was a complication in 12 patients. Overall incidence of early and late OHSS was 5.6% and 3.7% respectively. None of the patients developed OHSS twice (in a subsequent cycle). Both the groups were comparable in terms of patients' age, etiology of infertility and occurrence of polycystic ovaries.

COH Outcomes

Among 18 patients who developed early OHSS, 11 patients (61.1%) used GnRH agonist protocol and eight patients (38.9%) underwent GnRH antagonist protocol. In late group, GnRH agonist protocol was used in eight patients (66.7%), whereas four patients (33.3%) were selected for antagonist protocol. There were no significant differences in stimulation protocols between the early and late groups. The duration of stimulation and total doses of gonadotropin was similar between the two groups. The number of follicles on the day of hCG administration was significantly higher in the early group than in the late group(18.1± 5.36 Vs 12.0 ± 3.05, $p = 0.0004$). Similarly, the number of oocytes retrieved was also significantly higher in early OHSS cases than in the late group (11.5 ± 4.48 Vs 6.33 ± 1.72, $p = 0.001$). A significant difference was observed in the E2 levels on the day of hCG administration between the two groups (2778.5 ± 489.9 Vs 2200.4 ± 346.1, $p = 0.001$). No significant difference was found between both the groups with regards to number of embryos transferred. Embryo transfer was cancelled in 22.2% of cases in early group (Table1).

Severity of Disease and Hospital Courses

Late OHSS compared with early type had a significantly higher probability of being severe ($p = 0.025$), and the duration of hospitalization was also significantly longer in the late group patients (7.67 ± 2.0 days Vs 18.83 ± 2.29, $p < 0.01$). None of the patients in early group presented with severe OHSS. Only one patient with severe OHSS in late group needed readmission. The mean time between the oocyte pickup (OPU) and the day when the patients got admitted to the hospital was 7.9 days in early and 15.8 days in the late type (Table 2).

Table 1: Clinical characteristics and COH outcomes in early and late type of OHSS

Parameters	Early OHSS (N = 18)	Late OHSS (N = 12)	p-value
Age (yrs)	29.5 ± 3.09	29.8 ± 2.48	0.797
BMI (kg/m²)	24.6 ± 3.05	23.9 ± 2.55	0.549
Polycystic ovary pattern on USG n (%)	4 (22.2)	3 (25)	0.860
Type of stimulation protocol			
Agonist n (%)	11(61.1)	8 (66.7)	0.858
Antagonist n (%)	7(38.9)	4 (33.3)	
Total dose of gonadotropins used (IU)	1430.3 ± 288.7	1411.2 ± 356.5	0.873
E2 levels on day of hCG (pg/ml)	2778.5 ± 489.9	2200.4 ± 346.1	0.001
No. of follicles on day of hCG	18.1 ± 5.36	12.0 ± 3.05	0.0004
No. of oocytes retrieved	11.5 ± 4.48	6.33 ± 1.72	0.0001
Cancellation of embryo transfer n (%)	4 (22.2)	0	0.079
No. of embryos transferred	2.17 ± 1.24	2.75 ± 0.45	0.285

Table 2: Hospital courses in clinically pregnant patients with early and late type of OHSS

Parameters	Early OHSS (N = 18)	Late OHSS (N = 12)	p-value
Severity of OHSS			
Mild n (%)	11 (62)	2 (17)	0.016
Moderate n (%)	7 (38)	7 (58)	0.296
Severe n (%)	0	3 (25)	0.025
No. of days after OPU until admission	7.94 ± 2.77	15.8 ± 1.46	< 0.0001
No. of days of hospitalization	7.67 ± 2.0	18.83 ± 2.29	< 0.01
No. of patients needing readmission	0	1	0.213

Pregnancy Outcome

All cycles in which late OHSS occurred showed positive hCG test as compared to only 27.8% cases in early group ($p < 0.001$). Clinical pregnancy rate was also found to be significantly high ($p < 0.001$) in late group. This is attributed to the slightly higher miscarriage rate (though not statistically significant) in early group than in the late group

Table 3: Pregnancy outcome in early and late type of OHSS

Parameters	Early OHSS (N = 18) n(%)	Late OHSS (N = 12) n(%)	p-value
No. of positive hCG test	5 (27.8)	12 (100)	< 0.001
Preclinical miscarriage	2 (11.1)	1 (8.3)	0.804
Clinical pregnancy	3 (16.7)	11 (92.7)	< 0.001
Clinical miscarriage	0	0	-
Ectopic pregnancy	0	0	-
Singleton pregnancy	2 (66.7)	5 (45.5)	0.707
Multiple pregnancy	1 (33.3)	6 (54.5)	0.707

(11.1% Vs 8.3%, p = 0.804). However, the multiple pregnancy rate was similar between the two groups (p = 0.707) as shown in Table 3.

DISCUSSION

Prevention and early recognition of OHSS are the most important tools for the patient's safety. Identifying at-risk patients is critical in the prevention of OHSS, as it enables changes to be made to the ovarian stimulation regimen and / or other preventative measures. There are a number of well-established primary risk factors for the development of OHSS, including young age, polycystic ovary syndrome (PCOS) and a history of an elevated response to gonadotropins, *i.e.*, prior hyper-response / OHSS[3,16,17]. Secondary risk factors include absolute levels or rate of increase of serum E2, follicular size , and number of oocytes collected[16,18].

Although complete prevention of OHSS is still not possible, with early identification of potential risk factors and careful clinical management of all patients undergoing ovarian stimulation regimens, the incidence of OHSS can be significantly reduced. The following primary preventative strategies have been assessed: reducing exposure to gonadotropins, GnRH antagonist protocols, avoidance of hCG for LPS and *in vitro* maturation and insulin-sensitizing agents[19,20,21]. Secondary preventive strategies include coasting, reduced dose of hCG, GnRH agonist for triggering ovulation, intravenous albumin and hydroxyethyl starch, dopamine agonists, cryopreservation of all embryos and cycle cancellation[16,22,23,24].

Most OHSS can be managed on an outpatient basis, with oral analgesics and patient education regarding indicators of worsening illness that may require more aggressive intervention. Symptomatic relief of moderate OHSS with antiemetics and stronger analgesics should be accompanied by careful monitoring, including physical examination, ultrasound, weight measurement, and laboratory determination of hematocrit, electrolytes, and serum creatinine, ideally on a daily basis. Severe OHSS requires hospitalization, iv fluid management, ascites drainage, and prophylactic measures to prevent thromboembolism[12-14].

Lyons *et al* were the first to describe that OHSS occurs as two distinct clinical entities depending on the timing of onset. These forms differ in their patient characteristics, ovarian response parameters, relationship to pregnancy and clinical severity[6,7]. The common denominator of the disease is the multifollicular growth and supraphysiologic production of VEGF under the prolonged effect of hCG. The released vasoactive factor above a certain threshold induces significant vascular hyperpermeability. In early OHSS, because of the higher number of follicles (compared with late OHSS) and the bolus injection of hCG, this threshold is reached at an earlier stage whereas in the late type, gradual production of hCG by the implanting trophoblast leads to late presentation of the disease[8].

In our study, late OHSS presented with more severe disease and the duration of hospitalization was also longer in late group than the early group. These findings are concordant with those of previous studies[6,7]. The severity of OHSS was also significantly different between multiple pregnancies and singleton, and this result suggests that severity of OHSS is dependent on the incidence of multiple pregnancies in any type of OHSS[7]. In multiple pregnancies, higher levels of hCG leads to more production of vasoactive factors and contributes to the occurrence of more severe disease. The sustained action of rising hCG might also explain the higher severity of late OHSS.

In accordance with Papanikolaou *et al*, we found that the number of follicles and the estradiol concentration on the day of hCG production and the number of oocytes retrieved were statistically significantly higher in early OHSS cases than in the late group[8,18]. This suggests that the magnitude of preovulatory response to stimulation is an important determinant of the occurrence of early OHSS whereas late OHSS is not related to the ovarian response. These factors either in combination or alone can be used in identifying the patients at risk of developing early OHSS.

Our study is a prospective study, whereas most of the studies published in the literature are retrospective. The main limitation of our study is the absence of a non-OHSS group as control and its small sample size.

CONCLUSION

Our study concluded that the factors related to ovarian stimulation like the number of follicles, E2 levels on the day of hCG administration and the number of oocytes retrieved can serve as a useful guide in identifying the patients who are at the risk of development of early OHSS. However, these parameters may not be useful for the prediction of late OHSS. Although late OHSS cases are invariably

associated with conception, rate of occurrence of multiple pregnancy remains same in both the groups. Late OHSS is more likely to be severe and needs prolonged hospitalization than the early OHSS.

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Original Article

The Effect of Lornoxicam with Intravenous Regional Anesthesia on Intraoperative and Postoperative Analgesia for Forearm Surgery

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ABSTRACT

Objective: To evaluate the effect of lornoxicam added to lignocaine for intravenous regional anesthesia (IVRA)
Design: Prospective, randomized, double-blind controlled study
Setting: King Fahd Hospital, University of Dammam, Saudi Arabia
Subjects and Methods: Forty patients scheduled for upper limb surgery under IVRA were randomly allocated into two groups (20 patients per group) during the period from August 2010 to November 2011
Intervention(s): All patients received 4 mg/kg body weight lignocaine in 40 ml solution plus 3 ml of study solution containing either normal saline (control group) or lornoxicam 12 mg (IVRA- L group). Hemodynamic changes, sensory and motor block onset time, intraoperative and postoperative analgesia and total analgesic drug required in first 24 hours were observed.
Main Outcome Measure(s): Onset of sensory and motor block, requirement of intraoperative fentanyl, incidence of tourniquet pain, requirement of postoperative analgesia in terms of paracetamol consumption
Results: Patients who received the lornoxicam (IVRA-L group) had earlier onset of sensory and motor block ($p < 0.001$) and less requirement of intraoperative fentanyl ($p < 0.001$). Lornoxicam group patients tolerated tourniquet pain better ($p < 0.001$) and had better postoperative analgesia for first 24 hours ($p < 0.0005$).
Conclusion: Lornoxicam 12 mg is a beneficial addition to IVRA. It shortens the sensory and motor block onset time and increases the intraoperative and postoperative analgesia without any side effects. We observed that among non-steroidal anti inflammatory drugs (NSAIDs), lornoxicam is a very effective and safe adjunct to lignocaine for IVRA in upper limb surgery.

KEY WORDS: lignocaine, lornoxicam, postoperative pain, tourniquet pain

INTRODUCTION

Intravenous regional anesthesia (IVRA) is a simple, reliable, cost-effective technique for short duration upper limb surgical procedures. This technique is a safe local anesthetic technique[1]. The technique can be used for ambulatory surgery[2,3]. Adjuncts to local anesthetics for IVRA have been used to improve the quality of surgical analgesia, decrease tourniquet pain and improve postoperative analgesia[4-5]. In various previous studies on IVRA, non-steroidal anti inflammatory drugs (NSAIDs) such as ketorolac[6], tinoxicam[7-8] have been demonstrated to improve analgesia. In this study, we evaluated the clinical effect of lornoxicam added to lignocaine for forearm surgery using IVRA as the anesthetic technique.

Lornoxicam is a new addition to NSAIDs of the oxicam group. Lornoxicam has analgesic, antipyretic and anti-inflammatory properties. Lornoxicam is a potent analgesic with excellent anti-inflammatory properties in a range of painful and / or inflammatory conditions, including postoperative pain[9]. It is available in oral as well as parenteral form. It is rapidly eliminated and has a plasma half life of 3 - 5 hours[10], which suggest its suitability for acute post operative pain management[11]. Wound infiltration with lornoxicam with lignocaine improves postoperative pain control and patient comfort. *In vitro* experimental studies have demonstrated that lornoxicam is 100 times more potent than tenoxicam and 40 times more potent than peroxicam in its ability to inhibit cyclooxygenase[12].

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Lornoxicam is as effective as morphine and better tolerated when administered with patient-controlled analgesia even after laminectomy and discectomy[13]. Lornoxicam decreases the need for opioids in comparison to use of either drug alone, suggesting a local effect. Lornoxicam has side-effects similar to other NSAIDs, most commonly mild gastrointestinal disorders like nausea, diarrhea and headache. Severe but seldom side-effects include bronchospasm and may cause Stevens–Johnson syndrome. Lornoxicam is contraindicated in patients who are sensitive to NSAIDs, possible reasons including salicylate sensitivity, gastrointestinal bleeding and other bleeding disorders, and severe impairment of heart, liver or kidney function. Lornoxicam is not recommended during pregnancy and breast feeding and is contraindicated during the last trimester of pregnancy.

In this study, we evaluated the clinical effect of lornoxicam added to lignocaine using IVRA as anesthetic technique on intra and postoperative analgesia, sensory and motor block onset time and total consumption of analgesic drugs in first 24 hours after forearm surgery.

SUBJECTS AND METHODS

This study is a prospective, randomized and double-blinded study conducted during the period from February 2010 to December 2011 at King Fahd Hospital, University of Dammam, Saudi Arabia. Ethical committee approval was taken from University of Dammam ethics committee. Forty ASA I–II patients, aged 18 to 70 years of either sex scheduled for routine or emergency forearm surgery (*i.e.*, trauma and other orthopedic procedure under one hour duration, carpal tunnel, trigger finger, and tendon release, small skin grafting for the forearm, *etc*). Patients with sickle cell anemia, or history of drug allergy, and Reynaud's disease were excluded from the study. Informed consent was taken from every patient. Patients were randomly divided into two groups by computer generated list with 20 patients in each group. All the patients were premedicated with intravenous midazolam 0.10 mg/kg body weight. Fifteen minutes after premedication the patients were taken to the operating room.

In the operating room, all standard monitors including blood pressure (BP), oxygen saturation (SpO_2), and ECG (HR and rhythm) were applied. A small 22 gauge cannula was placed in a dorsal vein of the operative hand. The operative arm was elevated for three minutes and exsanguinated with an Esmarch bandage; a pneumatic tourniquet was then placed around upper arm, and proximal cuff was inflated to 250 mmHg. Circulatory isolation of the arm was verified by inspection, absence of radial pulse, and loss of pulse oximetry tracing in the index finger of the ipsilateral side. Identical syringes containing each drug was taken according to the study design. Drugs were prepared and concealed by an anesthesia resident not involved in any other part of the study. Another anesthesiologist blind to both groups and drug allocation was responsible for application of the concealed syringes and recording all data. The syringes were containing 4 mg/ kg lignocaine 2% diluted with saline to a total volume of 40 ml in both groups for IVRA. Group I (control group) received normal saline 0.9% 3 ml added to the IVRA solution; Group II (IVRA-L group) received lornoxicam 12 mg in 3 ml added to the IVRA solution.

We assessed the sensory block by a pinprick performed with a 23-gauge short-beveled needle every minute. Patient response was evaluated in the dermatomal sensory distribution of the ulnar, median, and radial nerves. Sensory block onset time was considered as the time elapsed from injection of drug to sensory block achieved in all dermatomes. Motor function was assessed by asking the patients to move his / her wrist and fingers, and complete motor block was noted when there is no voluntary movement. Motor block onset time was the time elapsed from injection of drug to complete motor block.

Once the sensory and motor blocks were complete, a second pneumatic tourniquet was applied below and distal to the first tourniquet and inflated to 250 mmHg. The proximal tourniquet was then deflated and removed. Surgery was allowed to start 10 minutes after the distal tourniquet inflation in all patients. Mean arterial blood pressure, heart rate, SpO2 and visual analogue scale (VAS) scores (0 = no pain and 100 = worst pain imaginable) was monitored before and after tourniquet application, at 5, 10, 20 and 30 minutes after injection of the anesthetic. Vital signs and pain score were observed and recorded after release of the tourniquet, postoperative 30 minutes and 2, 4, 6, 8, 12 hours and 24 hours by an anesthesiologist who was blinded to study. During surgery, if the pain score was > 30 on the VAS due to tourniquet or due to surgical pain, patients were given fentanyl 1 mcg/kg and the total administered dose and requirement time was noted. However, in any case the tourniquet was not deflated before 30 minutes after giving the drugs and was not inflated for more than 90 minutes. At the end of surgery, the tourniquet deflation was performed by the cyclic deflation technique.

Postoperatively patients were to receive 1 gram paracetamol orally when VAS was > 30 and the total paracetamol consumption 24 hours postoperatively was recorded. Skin rash, gastric discomfort, tinnitus, nausea and other side effects were also noted if encountered during the first 24 postoperative hours in the ward.

Table 1: Showing demographic data and operative characteristics. Values are expressed in mean ± SD (standard deviation)

Parameters	Control Group n = 20	IVRA-L Group n = 20	p-value
Age (yr)	37.4 ± 10.27	37.6 ± 10.10	0.95
Gender (M/F)	11/9	8/12	0.95
Weight (kg)	76.3 ± 8.72	77.7 ± 9.17	0.62
Duration of surgery (min)	44.1 ± 11.29	45.4 ± 6.36	0.66
Type of surgical procedure (trigger finger, carpal tunnel, tendon release, K wire fixation, ganglion removal)	4/6/5/5	3/9/5/3	0.76

IVRA = intravenous regional anesthesia; M/F = male/female

Statistical Analysis

In our previous study, sample size was selected to detect a mean reduction of 20% in the tourniquet tolerance time. Seventeen patients in each group were required based on type I error of 0.05 and type II error of 0.20. Power analysis was based on the study of hospital data of intravenous regional anesthesia. Two sample size estimations were performed. Both sample size estimation revealed a similar number and we decided to randomize 20 patients per group to be on safer side.

The gender of the patients and type of surgery were expressed by chi square test. All data were expressed as mean ± SD (standard deviation) and analyzed by one way analysis of variance (ANOVA) test. Then the difference was calculated by post hoc testing (Newman-Keuls test). A p-value of < 0.05 was considered significant and a p-value of < 0.001 as highly significant. Analysis was performed using the Statistical Package for Social Sciences Version 6.0 for windows (Stat soft, Inc).

Table 2: Onset times of sensory and motor block. Values are expressed in Mean ± SD

Parameters	Control Group n = 20	IVRA-L group n = 20	p-value
Sensory block onset time (min)	3.74 ± 0. 90	2.63 ± 0.75	< 0.001
Motor block onset time (min)	4.33 ± 0.78	2.93 ± 0.81	< 0.001

IVRA = intravenous regional anesthesia

RESULTS

In both groups, demographic data were similar for mean age, body weight and sex ratio. There was no significant difference between type of surgical procedure, duration of surgery and tourniquet time. There was no significant difference in both groups when the heart rate, blood pressure and pulse oxymetry at any intraoperative and postoperative period were compared ($p > 0.05$, Table 1).

Table 2 shows that the sensory and motor onset time in IVRA-L group was 2.63 ± 0.75 and 2.93 ± 0.81 minutes respectively and in control group was 3.74 ± 0.99 and 4.33 ± 0.78 minutes respectively. Sensory and motor onset time is significantly much shorter in the lornoxicam group ($p < 0.001$). The appearance of pain (Table 3) was significantly much delayed in IVRA-L group (53.9 ± 8.3 minutes) in comparison to control group (45 ± 5.4 minutes, $p < 0.001$). Intraoperative fentanyl requirement in control group was 72.25 ± 20.2 mcg, while in the IVRA-L group the consumption of fentanyl was only 21.25 ± 24 mcg. This was also highly significant.

Table 3: Comparison of analgesia time in the two groups. Values are expressed in mean ± SD

Parameters	Control Group n = 20	IVRA-L Group n = 20	p-value
Duration of intraoperative analgesia (min)	45 ± 5.4	53.9 ± 8.3	< 0.001
Fentanyl requiremnt (micrograms)	72.25 ± 20.2	21.25± 24	< 0.001

In the immediate first six hours postoperative (Table 4), VAS was also significantly much less in IVRA-L group (20.26 ± 18.74) as compared to control group (39.75 ± 74, $p < 0.001$). After six hours postoperatively VAS were 45 ± 13.67 in control group and 33.25 ± 12.19 in the IVRA-L group, which was less significant ($p < 0.05$). But as mentioned above, analgesia was much more significant. After 24 hours, the VAS were almost similar in both groups and there were no

Table 4: Post operative pain score in mm in first 24 hours (mean ± SD) in both groups (n = 20)

Groups	Pain score in mm by VAS		
	Just after tourniquet release	After 6 hours	After 24 hours
Control Gp	39.75 ± 18.74	45 ± 13.67	24 ± 11.88
Lornoxicam Gp	20.26 ± 13.50	33.25 ± 12.19	21.5 1± 0.4
p-value	0.001	0.007	0.483

VAS = visual analogue scale, Gp = group

Table 5: Total paracetamol (1gram tablets) oral consumption in post operative 24 hours. Values are shown as (mean ± SD)

Parameters	Control Group n = 20	IVRA-L group n = 20	p-value
Postoperative oral paracetamol consumption (No. of times)	4.2 ± 1.74	1.75 ± 1.1	< 0.0005

significant differences ($p > 0.05$). Table 5 shows that the total paracetamol requirement (number of times) was 1.75 ± 1.1 in IVRA-L group and 4.2 ± 1.74 in the control group which was highly significant ($p < 0.0005$).

DISCUSSION

IVRA was first described almost 100 years back in 1908 by August Bier[14]. Since then, various methods used to reduce the tourniquet pain during IVRA have generally been unsatisfactory. Tourniquet-related pain is the main factor limiting the extensive use of IVRA techniques in surgical procedures involving the extremities[15]. This distress may be caused due to multiple factors including neuropathic pain produced by nerve compression, stimulation of the nerve endings in the cutaneous tissue[16], skeletal muscle ischemia[17] and local metabolic changes[18]. We found that addition of lornoxicam is significantly effective in enhancing the analgesia time or tourniquet time as well as postoperative analgesia. There is much reduction of postoperative analgesic drug requirement. In previous studies when lornoxicam was added as an additive to lignocaine, the dose used was 7 or 8 mg only. But we used 12 mg lornoxicam added to lignocaine solution used for IVRA. This could be the reason for our better result and we did not notice any drug or dose related complications. The pH of iv lornoxicam form is approximately 8.7 and from a previous study, it was found that the pH of lornoxicam–lignocaine mixture was 7.6 and the pH of the lignocaine solution alone was 6.7[19]. It is thus possible that alkalinization of local anesthetic with lornoxicam might contribute to faster sensory and motor block onset times by increasing the proportion of free base. One previous study demonstrated the potential intraoperative benefit of NSAIDs added to local anesthetic. They added 30 mg ketorolac to IVRA solution to assess the tourniquet pain and pain at operative site by visual analog scale. In first 24 hour postoperatively, there were significantly less pain scores in ketorolac group, together with less requirement of alfentanyl for early postoperative pain and significantly less requirement of analgesic tablets[20]. One other study also explained that NSAIDs decrease the synthesis of inflammatory mediators and afferent nociceptive signals arising from the site of surgery. The major analgesic effect of NSAID is assumed to be due to COX-2 inhibition. COX-2 is an inducible molecule which takes several hours to induce inflammatory pain[21]. This mechanism is not supported by our clinical study and adding lornoxicam to IVRA has an immediate onset of action. There must be some other mechanism involved. In various previous studies, there is an effort to explain this mechanism. In one study, it is said that the opening of the K^+ channels located in the primary afferent nerve endings produces antinociception and represents an important step in the peripheral antinociceptive effect of several NSAIDs[22]. In another study, it is said that the activation of the NO-cyclic GMP pathway could also induce antinociception through the opening of K^+ channels[23]. Lornoxicam might produce a peripheral analgesic effect *via* NO–cGMP pathway and the opening of K^+ channels. Buritova and Bessonalso suggested that lornoxicam shows antinociceptive effect in predominantly peripheral site[24]. These mechanisms may explain why the analgesic effect of lornoxicam in IVRA is better than the systemic administration for tourniquet pain. Orthopedic operative procedures often cause severe pain. Hence 12 mg of lornoxicam with IVRA would be the optimal choice for relief of moderate to severe pain.

The limitation of this study is the relatively less number of patients. We recommend more prospective studies on this subject with more number of patients. Another limitation of this study is that we did not make another group with systemic intravenous administration of lornoxicam. Though our findings suggested that a local mechanism could be at least partly responsible for the analgesic effect of lornoxicam added to lignocaine during IVRA, it is still possible that lornoxicam analgesic effect occurs through systemic absorption.

CONCLUSION

The addition of lornoxicam to lignocaine with IVRA is significantly effective in shortening the sensory and motor block onset time and decreasing tourniquet pain of upper limb surgery. Lornoxicam is also a very effective adjunct to lignocaine for post operative analgesia.

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Original Article

Cardiovascular Disease and Colorectal Cancer: A Population-Based Observation in Taiwan

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ABSTRACT

Objective: To explore the relationship between cardiovascular disease and colorectal cancer in Taiwan

Design: Population-based cohort study

Subjects: Using database of the Taiwan National Health Insurance program from 2000 to 2006, 89,034 patients (35 years or older) with newly diagnosed cardiovascular disease (CVD) which included coronary artery disease, heart failure, cerebrovascular disease, peripheral atherosclerosis, or hypertension, and 89,034 control subjects without CVD were studied

Main Outcome Measures: The incidence of colorectal cancer at the end of 2009 and the association with CVD and other co-morbidities were determined

Results: The incidence of colorectal cancer was 1.19-fold higher in the CVD group compared with the non-CVD group (10.87 Vs 9.11 per 10,000 person-years, 95%CI = 1.05-1.36). After adjustment for covariates, no association was found between CVD and colorectal cancer (95%CI = 0.87-1.13). Men (HR = 1.53, 95%CI = 1.34-1.75), increasing age (HR = 1.07, 95%CI = 1.06-1.07), and colorectal adenoma (HR = 1.80, 95%CI = 1.06-3.05) were associated with colorectal cancer.

Conclusions: No association between cardiovascular disease and colorectal cancer is found. Men, increasing age, and colorectal adenoma correlate with the increased risk of colorectal cancer.

KEYWORDS: cardiovascular disease, colorectal adenoma, colorectal cancer

INTRODUCTION

Colorectal cancer is a relatively important public health issue, being the third most commonly diagnosed cancer after lung and breast cancers worldwide in 2008 and nearly 60% of cases occurring in industrialized countries[1]. Overall, there are almost one million new cases of colorectal cancer in the world each year that cause half a million deaths[1, 2].

Although the real cause of colorectal cancer remains unclear, recently, there is strong evidence linking metabolic syndrome and colorectal cancer[3-5]. In a study by Stocks *et al* in Sweden, men with metabolic syndrome were 1.25 times (95% CI: 1.18-1.32) and women with metabolic syndrome were 1.14 times (95% CI: 1.06-1.22) more likely to develop colorectal cancer[4]. Abdominal obesity and insulin resistance / hyperinsulinemia may play the pivotal roles between metabolic syndrome and colorectal cancer[6,7]. Currently, epidemiologic evidence is accumulating that metabolic syndrome is also related to the risk of cardiovascular disease (CVD)[8-11]. In a meta-analysis by Mottillo *et al*, subjects with metabolic syndrome were 2.35 times more likely to be associated with CVD (95% CI: 2.02 to 2.73), 2.27 times more likely to be associated with stroke (95% CI: 1.80 to 2.85) and 1.99 times more likely to be associated with myocardial infarction (95% CI: 1.61 to 2.46)[11]. In previous reviews, inflammatory process, endothelial dysfunction and atherosclerosis modulated by insulin-resistance are the major pathological at mechanisms linking metabolic syndrome and CVD[12,13]. According

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to the above findings, we made a hypothesis that there is an association between CVD and colorectal cancer. If this hypothesis is correct, early targeted intervention for CVD may correlate with risk reduction of colorectal cancer.

In Taiwan, colorectal cancer was the third leading cause of cancer deaths after liver and lung cancers and it accounted for 11.4% of all cancer deaths in 2010 (mortality rate 20.2 per 100,000 persons)[14]. CVD and cerebrovascular disease were the second and the third leading causes of death, and accounted for 10.8% and 7.0% of all deaths in Taiwan in 2010, respectively[14]. On the other hand, a cohort study by Chien *et al* in Taiwan showed that metabolic syndrome is associated with an increased risk for CVD[15]. To date, no evidence is available about the association between CVD and colorectal cancer in Taiwan. Therefore, we conducted this population-based cohort study from the National Health Insurance program database in Taiwan, to explore the following questions: (i) Is there is an association between CVD and colorectal cancer? (ii) What is the role of other co-morbidities on the risk of colorectal cancer?

SUBJECTS AND METHODS

Data sources

This cohort study used data from the National Health Insurance program in Taiwan. The insurance program details could be found in previous studies[16-20]. All types of personal identification on files connected with the present study were scrambled using surrogate identification numbers to secure patient privacy. This study was exempt from full review by the institutional review board.

Design

This cohort study would investigate whether patients with CVD were at an increased risk of colorectal cancer (International Classification of Diseases 9th Revision-Clinical Modification, ICD-9 codes 153 and 154, and A-code A093 and A094). In the CVD group we included subjects aged 35 years and older with a newly diagnosed of coronary artery disease (ICD-9 codes 410-414, and A-code A270 and A279), heart failure (ICD-9 codes 428), cerebrovascular disease (ICD-9 codes 430–438, and A-code A290-A294 and A299), peripheral atherosclerosis (ICD-9 codes 440-448, and A-code A300), or hypertension (ICD-9 codes 401-405, and A-code A260 and A269) between 2000 and 2006[21, 22]. In addition to ICD-9 codes, the A-code was also used to define diseases because it had been used before ICD-9 code was adapted in Taiwan. For each CVD patient, one subject without medical claims for CVD who was frequency matched with sex and age (every 5-year span) in the same period was randomly selected. An index date for the CVD patients was defined as their date of diagnosis. An index date was assigned for the corresponding comparison subjects as the middle date of the same index month as their matched CVD patients. Subjects diagnosed with previous cancers (ICD-9 codes 140 -208 and A-code A08X-A14X) before the index date were excluded from the study. Other co-morbidities before the index date were defined as follows: hyperlipidemia (ICD-9 codes 272.0, 272.1, 272.2, 272.3 and 272.4), obesity (ICD-9 codes 278.00 and 278.01, and A-code A183), diabetes mellitus (ICD-9 codes 250 and A-code A181), colorectal adenoma (ICD-9 codes 211.3 and 211.4), inflammatory bowel diseases (ICD-9 codes 555.X and 556.X), tobacco use (ICD-9 305.1), and alcoholism (ICD-9 codes 303, 305.00, 305.01, 305.02, 305.03 and V11.3, and A-code A215). The potentially colon-related medications included were as follows: statin, aspirin, other non-steroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 inhibitors (COX-2 inhibitors), estrogen, and metformin.

Diagnosis of colorectal cancer was used as the study end-point. Both CVD and non-CVD groups were followed up to determine the incidence of colorectal cancer until a subject received the diagnosis of colorectal cancer, or until the end of 2009, or until censored because of withdrawal from the insurance program.

Statistical analysis

Chi-square test and Student's t-test were used to compare the differences between the CVD group and the non-CVD group regarding socio-demographic characteristics and co-morbidities. The incidence rate was calculated as the number of colorectal cancer cases identified during the follow-up, divided by the total person-years for each group by sex, age, and follow-up years. Cox proportional hazard models were used to estimate the hazard ratios (HR) with 95% confidence intervals, which determined the association between CVD and colorectal cancer. The risk of colorectal cancer associated with co-morbidities and potentially colon-related medications were also estimated. The risk of developing colorectal cancer associated with five types of cardiovascular diseases was also measured. All analyses were performed using SAS software version 9.1 (SAS Institute Inc., Cary, NC), and the statistical significance level was set at two-sided $p < 0.05$.

RESULTS

Baseline characteristics of the study population

From the claims data of 2000 - 2006, 89,034 patients with CVD met the eligibility criteria; 89,034 subjects in the non-CVD group were used as control (Table 1). The two groups were similar in distributions of sex and age-group. Hyperlipidemia, obesity, diabetes mellitus, colorectal adenoma, inflammatory bowel diseases, tobacco use, and alcoholism were more prevalent in

Table 1: Baseline characteristics between cardiovascular disease group and non-cardiovascular disease group

Patient Characteritics	Cardiovascular disease				p-value
	No		yes		
	n	%	n	%	
Sex					1.00
Women	41,867	47.0	41,867	47.0	
Men	47,167	53.0	47,167	53.0	
Age group (years)					1.00
35 - 49	39,020	43.8	39,020	43.8	
50 - 64	32,557	36.6	32,557	36.6	
≥ 65	17,457	19.6	17,457	19.6	
Mean (SD) (years) *	53.8	12.1	54.0	12.0	0.003
Co-morbidities prior to index date					
Hyperlipidemia	5,361	6.02	13,090	14.7	<0.0001
Obesity	95	0.11	256	0.29	<0.0001
Diabetes mellitus	4,080	4.58	9,224	10.4	<0.0001
Colorectal adenoma	488	0.55	667	0.75	<0.0001
Inflammatory bowel diseases	2,038	2.29	2,773	3.11	<0.0001
Tobacco use	170	0.19	318	0.36	<0.0001
Alcoholism	499	0.56	1,002	1.13	<0.0001

Chi-square test and *Student's t-test comparing patients with and without cardiovascular disease

the CVD group than in the non-CVD group at baseline ($p < 0.0001$).

By the end of follow-up, the incidence of colorectal cancer was higher in the CVD group than in the non-CVD group (10.87 Vs 9.11 per 10,000 person-years, 95%CI =1.05-1.36, Table 2). The incidence of colorectal cancer, as classified by sex, age and follow-up period, was higher in subjects with CVD. Subjects with diagnosis duration of CVD more than two years had higher colorectal cancer risk (incidence rate ratio = 1.26, 95% CI = 1.07-1.47), when compared with the non-CVD group.

Colorectal cancer associated with co-morbidities

After adjustment for covariates, the multivariate Cox proportional hazard regression analysis revealed that no association was found between CVD and colorectal cancer (95%CI = 0.87-1.13, Table 3). Men (HR = 1.53, 95%CI = 1.34 - 1.75), increasing age (HR = 1.07, 95%CI = 1.06-1.07), and colorectal adenoma (HR = 1.80, 95%CI = 1.06 - 3.05) were found to be associated with colorectal cancer. No association was found between colon-related medications and colorectal cancer.

Table 2: Incidence density of colorectal cancer estimated by socio-demographic characteristics between cardiovascular disease group and non-cardiovascular disease group

Patient Characteritics	Non-cardiovascular disease				Cardiovascular disease					
	n	case	Person years	Incidence rate*	n	case	person years	Incidence rate*	IRR†	(95% CI)
All	89,034	382	4,19,106	9.11	83,034	606	5,57,437	10.87	1.19	(1.05-1.36)
Sex										
Women	41,867	134	1,98,640	6.75	41,867	225	2,68,231	8.39	1.24	(1.00-1.54)
Men	47,167	248	2,20,467	11.25	47,167	381	2,89,206	13.17	1.17	(0.99-1.37)
Age group (years)										
35 - 49	39,020	63	2,16,288	2.91	39,020	81	2,51,275	3.22	1.11	(0.80-1.54)
50 - 64	32,557	159	1,47,073	10.81	32,557	239	2,05,657	11.62	1.08	(0.88-1.31)
≥ 65	17,457	160	55,746	28.70	17,457	286	1,00,505	28.46	0.99	(0.82-1.20)
Time since the diagnosis of CVD (years)										
< 2	89,034	151	1,59,685	9.46	89,034	177	1,74,133	10.16	1.07	(0.87-1.34)
≥ 2	71,893	231	2,59,421	8.90	85,769	429	3,83,304	11.19	1.26	(1.07-1.47)

†IRR (Incidence risk ratio) = Cardiovascular disease vs non - cardiovascular disease (95 % CI), CI= Confidence interval

* Incidence rate = Per 10,000 person-years

Table 3: Adjusted hazard ratios and 95% confidence intervals of colorectal cancer associated with cardiovascular disease and covariates

Variables	Crude	Adjusted	
	HR (95% CI)	Model 1 (95% CI)†	Model 2 (95% CI)††
Sex			
Women	1.00	1.00	1.00
Men	1.61 (1.41 - 1.83)	1.57 (1.38 - 1.78)	1.53 (1.34 - 1.75)
Age (per one year)	1.07 (1.07 - 1.08)	1.07 (1.06 - 1.07)	1.07 (1.06 - 1.07)
Cardiovascular disease			
No	1.00	1.00	1.00
Yes	1.18 (1.04 - 1.34)	0.98 (0.86 - 1.12)	0.99 (0.87 - 1.13)
Diabetes Mellitus			
No	1.00	1.00	1.00
Yes	1.43 (1.16 - 1.76)	1.17 (0.95 - 1.45)	1.18 (0.96 - 1.46)
Colorectal Adenoma			
No	1.00	1.00	1.00
Yes	2.43 (1.44 - 4.13)	1.77 (1.05 - 3.01)	1.80 (1.06 - 3.05)
Ever use of medications			
Other NSAIDs			
No	1.00	--	1.00
Yes	0.81 (0.67 - 0.99)	--	0.97 (0.79 - 1.18)
COX-2 Inhibitors			
No	1.00	--	1.00
Yes	1.22 (1.03 - 1.44)	--	0.95 (0.80 - 1.13)
Estrogen			
No	1.00	--	1.00
Yes	0.45 (0.28 - 0.73)	--	0.71 (0.44 - 1.16)

Hyperlipidemia, obesity, inflammatory bowel diseases, tobacco use, alcoholism, statins, aspirin, and metformin did not show a statistical significance in crude analysis.
†Model 1, adjusted for age, sex, and co-morbidities
††Model 2, adjusted for age, sex, co-morbidities and medications

Sub-analysis of the association between fives types of cardiovascular diseases and colorectal cancer

As shown in Table 4, the association between different cardiovascular diseases and colorectal cancer was further analyzed. As a reference of non-CVD group, no association was detected between any type of cardiovascular diseases and colorectal cancer.

DISCUSSION

The topic is completely novel. To the best of our knowledge, this is the first study that explores the association between CVD and colorectal cancer. In addition, because only few related studies could be found, we cannot indulge in a more detailed discussion. Though the incidence of colorectal cancer was higher in the CVD group than in the non-CVD group in the present study, after adjustment for covariates, no association was found between CVD and colorectal cancer. Even in sub-analysis, we could not detect an association between any type of CVD and colorectal cancer. According to previous literature, abdominal obesity and insulin resistance / hyperinsulinemia may play key roles between metabolic syndrome and colorectal cancer[6, 7]. Metabolic syndrome is also related

Table 4. Cox model hazard ratios and 95% confidence intervals of colorectal cancer associated with fives types of cardiovascular diseases

Type of cardiovascular disease	N	Case	Person years	Incidence rate *	Crude HR	(95% CI)	Adjusted HR†	(95% CI)
Non-CVD as reference	89,034	382	4,19,106	9.11	1.00		1.00	
Coronary artery disease	19,834	135	1,29,126	10.45	1.15	(0.95 - 1.40)	0.98	(0.80 - 1.20)
Heart failure	3,031	28	16,671	16.80	1.86	(1.27 - 2.73)	1.14	(0.77 - 1.68)
Cerebrovascular disease	10,148	80	59,518	13.44	1.47	(1.15 - 1.87)	0.97	(0.76 - 1.25)
Peripheral atherosclerosis	7,538	37	47,963	7.71	0.85	(0.61 - 1.20)	0.90	(0.64 - 1.27)
Hypertension	54,152	370	3,38,416	10.93	1.18	(1.03 - 1.37)	1.00	(0.86 - 1.16)

†Adjusted for sex, age, diabetes mellitus, colorectal adenoma, other NSAIDs, COX-2 inhibitors and estrogen
* Incidence rate: per 10000 person-years

to the risk of CVD[8-11]. However, we could not find the evidence to support the association between CVD and colorectal cancer in this study. Because this was an observational study, we cannot provide any plausible explanation regarding these results.

This present study also demonstrated a significant association between colorectal cancer and increasing age (HR = 1.07), male gender (HR = 1.53), and colorectal adenoma (HR = 1.80). These findings were compatible with previous studies[23-26].

Some limitations should be addressed. First, because there was no record about insulin level or metabolic syndrome in this database, we could not make a direct link between insulin, metabolic syndrome, colorectal cancer and CVD. Second, no data on specific diet (red meat *etc*), body mass index (BMI), or family history were included. This was due to the inherent limitation of this database. While we included obesity as a cofactor by using ICD-9 codes, it did not show a significant association with colorectal cancer in crude analysis. Third, the results of this present study are preliminary. Thus, clinical significance of this topic cannot be clearly established. Further studies are needed to confirm the results of this study.

CONCLUSION

Our study did not detect any association between CVD and colorectal cancer. Whereas, gender (male), increasing age, and colorectal adenoma are found to be associated with colorectal cancer.

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Conflict of Interest : The authors disclose no conflicts of interest.

Declaration : The first two authors contributed equally to this study.

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Original Article

Surgical Repair of Penile Fracture

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ABSTRACT

Objective: To evaluate the preoperative diagnostic methods and the outcome of surgical treatment of penile fractures in patients treated at our institution
Design: Retrospective study
Setting: Department of Surgery, Urology Unit, Al-Jahra Hospital, Kuwait
Subjects and Methods: Eighteen patients treated surgically for penile fracture during the period from October 2007 to June 2012 were included. The diagnosis of penile fracture was made on clinical grounds and penile ultrasonography. Patients were treated by immediate surgery. Corpus cavernosum tear was repaired with absorbable sutures.
Interventions: Surgical repair with absorbable sutures
Main Outcome Measures: Evaluation of preoperative diagnostic methods and the results of early surgical treatment
Results: Patients presented within 6 - 20 hours (median time 16 hours) after injury. With a mean follow-up of 18 months (range 12 to 24 months), all patients were able to achieve full erection. No penile deformities or penile plaques were reported.
Conclusion: Penile fracture represents a true urological emergency. In nearly all cases diagnosis can be made on typical history and clinical examination. Early surgical exploration and repair of tunica albuginea can result in good functional outcome.

KEY WORDS: penile deformity, penile fracture, surgical repair

INTRODUCTION

Penile fracture is a traumatic rupture of the tunica albuginea with subsequent subcutaneous hematoma with or without rupture of the corpus spongiosum and the urethra[1]. It occurs only with an erect penis when the tunica albuginea is attenuated and rigid. Other mechanisms of this injury include abnormal bending of the penis during masturbation, rolling over in bed onto the erect penis or forceful efforts to elicit detumescence[2]. The site of injury is variable, but mostly occurs near the base or mid-shaft region of the penis[3].

The patient typically hears a loud snapping sound associated with pain and rapid detumescence followed by penile deviation to the opposite side of the injury with ecchymoses and hematoma[4]. With small tears, angulations and hematoma formation may be minimal, making identification of the site of the injury difficult [5].

The majority of cases are not associated with urethral injuries; however, blood at the meatus often indicates urethral disruption. Many authors advocate the use of ultrasound (US) of the penis to help making a firm diagnosis[6]. By US, large tunical disruptions are easily identified as well as the size and the site of the hematoma; however, small tears remain and may be difficult to diagnose.

SUBJECTS AND METHODS

In all cases, diagnosis was made on the basis of typical history, physical examination, penile US imaging in all cases and retrograde urethrogram in three cases (where blood was found at the external meatus). Cracking sound was heard by all patients except two. Penile swelling was present in all patients mostly involving the whole penis. All patients underwent immediate surgery. The surgical technique used consisted of a subcoronal incision, with penile degloving and exposure of the corpora cavernosum and urethra. Bladder catheterization was routinely performed, after ruling out any urethral injury. The corpora cavernosa lesions were treated by interrupted absorbable sutures. Bladder catheter was maintained for 48 hours after the surgical procedure. Only one

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patient required Penrose #1 drain owing to large albuginea disruption and the presence of a large hematoma. The drain was withdrawn at hospital discharge. All patients were followed up in urology outpatient at variable intervals.

Table 1: Patients characteristics

Clinical parameters	No. of patients	(%)
Age (yrs)		
16 - 30	1	5.55
31 - 45	15	83.33
46 - 60	2	11.11
Duration		
< 6 h	2	11.11
6 - 24 h	16	88.88
> 3 days	-	-
Local findings		
Audible crackling sound	16	88.88
Deformity	8	44.44
Swelling	18	100
Pain	7	38.88
Etiology		
Fall onto erected penis	9	50
Sexual maneuvers	7	38.89
Penile manipulation	2	11.11
Diagnosis of penile tunica albuginea injury		
Penile-ultrasound	9	50
Penile-MRI	3	16.66
Only after exploration	6	33.33

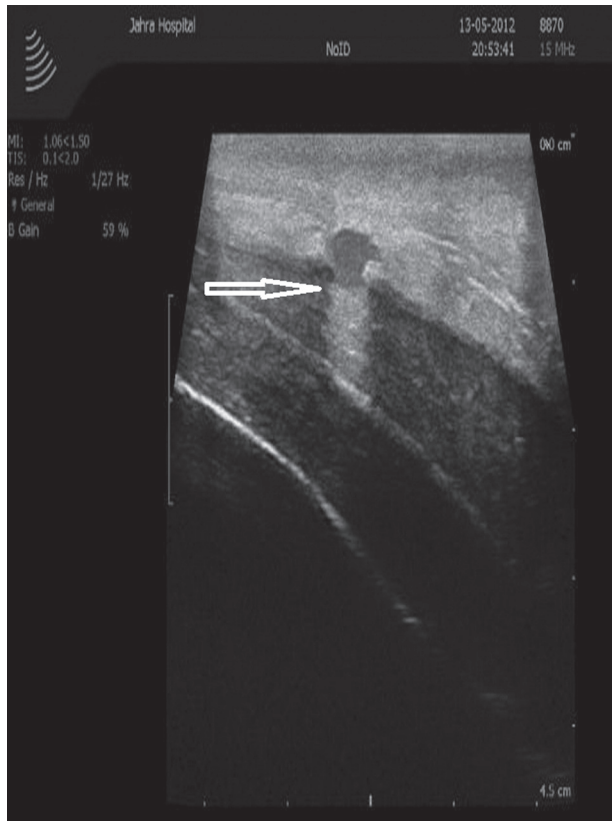

Fig. 1: Penile ultrasound: 0.5 cm injury in the tunica albuginea

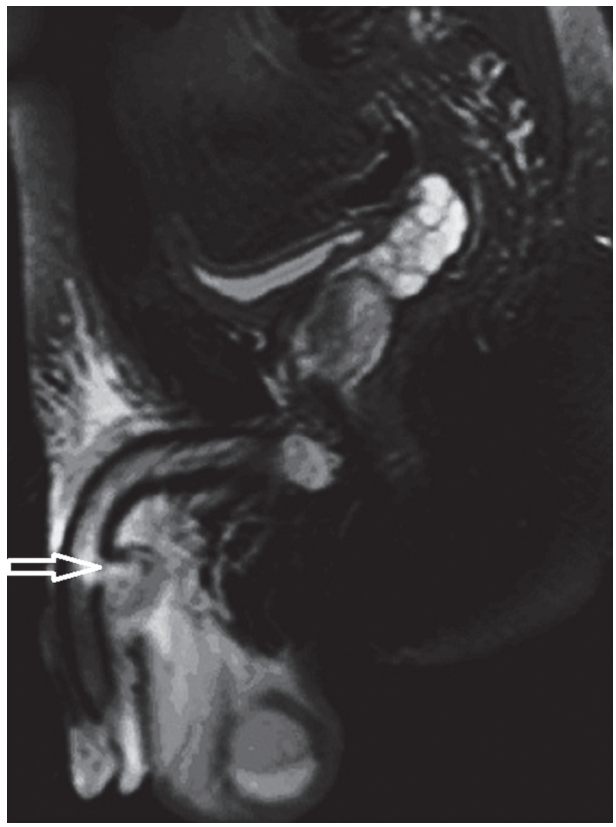

Fig. 2: Penile MRI (Sagittal T2WI): 1.5 cm injury in the tunica albuginea with penile hematoma

RESULTS

In a five years period (Oct 2007 - Jun 2012), eighteen patients aged 16 - 60 years (mean age 38 years) presented with penile fracture were hospitalized in the urology department of Al-Jahra hospital, Kuwait. Patient characteristics are shown in Table 1. The injury was due to fall onto erected penis in nine patients, sexual maneuvers in seven patients and penile manipulation in two patients.

The interval from injury to presentation ranged from 6 - 20 hours (median time 16 hours). Penile fracture was due to fall onto erected penis in nine patients (50%), sexual maneuvers in seven patients (38.89%), and manipulation in two patients (11.11%). All patients presented with unilateral corpus cavernosum lesion on the right side. Most tears were found at the proximal shaft. Only in five cases, the tears were on mid shaft and the dorsal penile vein was torn in one case. An albuginea disruption was confirmed by US study in nine cases (50%, Fig. 1) and by magnetic resonance imaging (MRI) in three cases (Fig. 2). In other's cases, it was not possible to determine the lesion, and the patient was submitted to surgical exploration that confirmed the condition. Lesion size ranged from 0.5 cm to 2.0 cm (mean 1.5 cm, Fig. 3 & 4). All corpora cavernosa lesions identified during surgical exploration were treated by

Fig. 3: 4 x 3 cm penile hematoma

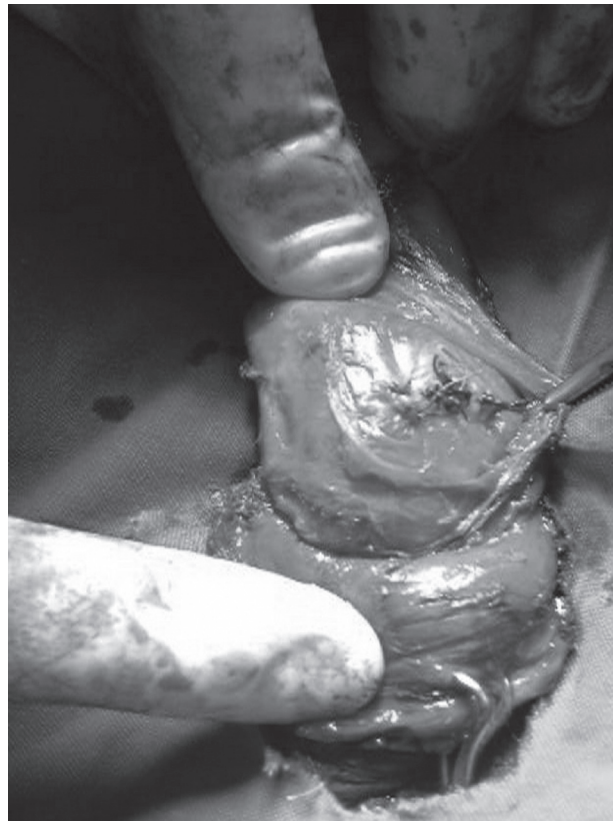

Fig. 5: Post-repair of the tunica-injury

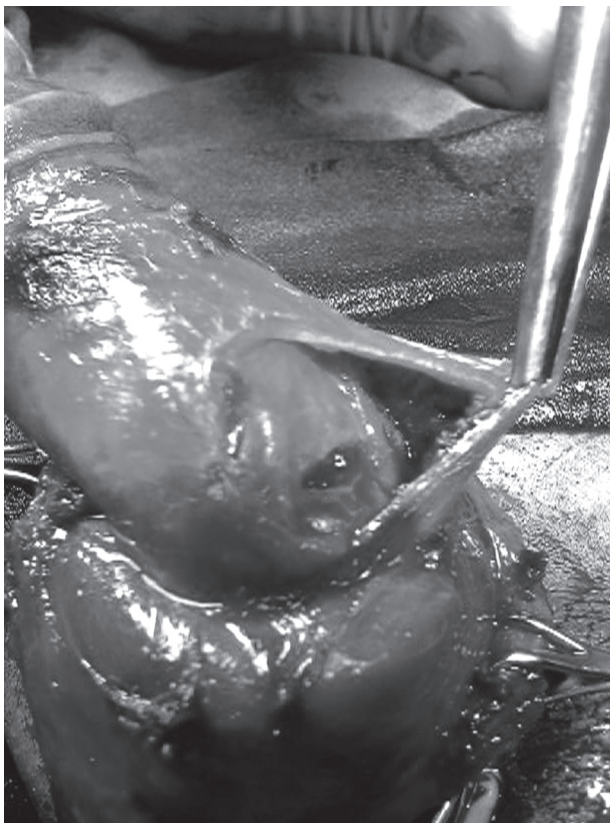

Fig. 4: Tear of the penile tunica albuginea

interrupted polyglactine 3 - 0 sutures (Fig. 5). The mean hospitalization time was three days (range 2 - 5 days). Mean follow-up after surgery was 18 months (range 12 to 24 months). All patients had good functional outcome of surgery and normal full erections. The statistical results are presented in Table 2.

Tabel 2 : Lesions found in patients presenting with penile fracture

Type of lesion	No. of patients	(%)
Corpous cavernosum only	17	94.45
Dorsal penile vein only	1	5.55
Urethral affection	-	-
Site of tunica tear		
Proximal shaft	13	72.22
Mid shaft	5	27.77
Length of tear		
0.5 - 1 cm	10	55.55
1.1 - 2 cm	6	33.33
> 2 cm	2	11.11

DISCUSSION

Penile fracture is a real urological emergency and is under-reported due to the shyness to describe it. Therefore, it leads to complications like erectile dysfunction later on[7,8]. Until the early 1980's, the management of penile fracture was highly controversial. Many conservative treatments had been

employed that included use of compression bandages, ice packs and anti-inflammatory agents and simple analgesia and sedatives to suppress erections[8]. Such conservative treatment is associated with significant complications such as delayed chordee and formation of a firm fibrous plaque similar to Peyronie's disease, which can occur in as much as 30 - 50% of cases[9]. However, the current standard of care is immediate surgical repair and decreased incidence of subsequent morbidity[9]. Repair can be done with absorbable or non-absorbable sutures with inverted knots. However, usage of non-absorbable suture material can leave knots that may be palpable and painful for the patient and his partner[10].

Fracture of the penis is an uncommon urological condition. It occurs when excessive force is applied to the long axis of the penis in an erect state resulting in rupture of the tunica albuginea of the corpus cavernosum[11].

Activities resulting in an erect state of penis like masturbation, self-manipulation, sexual intercourse, and rolling over in bed, can cause direct penile trauma and result in fractures[12]. The most common cause of penile fracture is sexual intercourse (33 - 58%). Increased use of pharmaceutical agents which enhance the duration of erection increases the chance of penile fractures[13]. In our study, the commonest cause of penile fracture was a fall onto an erect penis (50%).

Data from the patients' history and physical examination are always the cornerstone for correct diagnosis as sudden cracking sound is often heard followed by pain, rapid detumescence, swelling, and penile deformity[14].The site of the tear was diagnosed by the penile deviation away from the tear and was confirmed intraoperatively in most cases.

Adequate clinical examination may not always be possible or may be inconclusive, hence comes the role of imaging. An array of imaging modalities like cavernosography, US and MRI can be used to identify penile fractures. Soft tissue details in multiple planes are shown best by MRI, which demonstrates discontinuity of the normal low-signal intensity ring of the tunica albuginea on T2-weighted images after a tear (Fig. 5). Discontinuity between the corpus cavernosum and ischium also results in focal low signal intensity on T2-weighted images[15]. From a practical aspect, US scores over MRI in terms of cost, availability and time consumed for the procedure[16].

In our study, the diagnosis was mainly based on the history, clinical features and penile US imaging. Our operative plan was immediate exploration, debridement and primary surgical repair of the tear in the tunica albuginea. The prompt surgical intervention in this study caused no complications like hematoma, nodules or the development of significant penile curvature.

CONCLUSION

The incidence of penile fractures is on the rise due to the increased use of performance-enhancing drugs. An individual with a penile fracture should seek immediate medical care. Prompt diagnosis and surgical management is necessary to prevent undesirable complications and preserve penile function.

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Original Article

Comparison of Ectopic Pregnancy Treatment Modalities: Experience from a Tertiary Center

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ABSTRACT

Objectives: To review and analyze the outcomes of various treatment modalities in women with ectopic pregnancy (EP) in a tertiary center between January 2006 and February 2011
Design: Retrospective study
Setting: Duzce University Hospital, Turkey
Subjects and Methods: The medical records of 116 women diagnosed with EP were reviewed retrospectively. Women were grouped based on the treatment modality: Expectant (Group I), Medical treatment with methotrexate (Group II) and Surgical (salpingostomy and salpingectomy) (Group III). Demographic characteristics were analyzed and the success rates between the groups were compared.
Intervention: None
Main Outcome Measures: Success rates between groups based on treatment modality
Results: Success rates for expectant, medical management with single dose of methotrexate, salpingostomy and salpingectomy were 66.7%, 79%, 92.7% and 100%, respectively. There was no difference between the success rates of laparoscopic salpingostomy and single dose methotrexate ($p = 0.246$). Salpingectomy was more successful compared to expectant and medical managements ($p = 0.003$ and $p = 0.040$, respectively).
Conclusion: The highest success rate in EP was achieved by surgical treatment. However, expectant and medical treatment may eliminate the need for surgery in selected cases with low and / or decreasing initial β-hCG levels.

KEY WORDS: ectopic pregnancy, expectant management, methotrexate therapy, surgical treatment

INTRODUCTION

Ectopic pregnancy (EP) is the leading cause of maternal mortality in first trimester and it constitutes 75% and 90% of pregnancy related deaths in first and all three trimesters, respectively[1,2]. The incidence of EP has dramatically increased in the past few decades in developed countries from 0.5% in 1970 to 2% of pregnancies in 1992[3,4]. This is thought to be related to either the increase in the incidence of sexually transmitted disease or development of better diagnostic methods[5].

The surgical approach with laparotomy was the mainstay of the therapy in any clinical scenario before 1980's. Improvements in minimal invasive technology contributed to the increase in the success rate of laparoscopy approaching nearly to 96% in 1990's, so much so that it became the standard surgical management[6]. Meanwhile, the implementation of sensitive β - hCG assays and high resolution transvaginal ultrasonography to the diagnostic algorithm of EP made early diagnosis possible before rupture, enabling successful medical therapy with systemic or local methotrexate (MTX) either in a single or multiple dose protocol in hemodynamically stable women. Reported success rate of systemic MTX ranges between 65% and 95% and is comparable to that of laparoscopic salpingostomy in un-ruptured tubal EPs[6-8].

However, the implementation of these new therapeutic modalities brought new conflicts regarding the most convenient approach in terms of treatment efficacy, applicability regimen, dosing, future pregnancies, post-treatment tubal patency, persistent ectopic pregnancy rate, predictors of success and cost – effectiveness[6-8].

The aim of this study was to analyse the outcomes of various treatment modalities in EP focusing on un-ruptured tubal pregnancies treated in our clinic and review the relevant literature briefly.

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SUBJECTS AND METHODS

We retrospectively reviewed the medical records of women diagnosed with EP who were managed in the Obstetrics and Gynecology Department of Duzce University Hospital between January 2006 and February 2011. The study was approved by Duzce University Non-Invasive Human Research Ethics Committee.

The diagnosis of EP in our clinic is based on the results of a combination of serum β - hCG levels, transvaginal ultrasonography and / or histological findings of uterine curettage material. EP was diagnosed if serum β - hCG > 2000 mIU/ml with no intrauterine gestation visible at transvaginal ultrasonography. If β - hCG < 2000 mIU/ml, women were followed up at 48-hour intervals similar to the diagnostic procedure of Stoval *et al*[9]. (1) Pregnancy was considered intrauterine when there is > 60% increase in β - hCG 48 hours later and these women were followed up until β - hCG > 2000 mIU/ml to confirm intrauterine gestation by transvaginal ultrasonography. (2) If serum β - hCG levels were decreasing at follow-up, levels were continued to be checked serially until it becomes < 15 mIU/ml. These women were excluded from analysis since an aborting intrauterine pregnancy could not be excluded. However, if levels were increased by < 50% or reached a plateau in the next 48 hours, dilatation and curettage (D&C) was performed with informed consent of patient. EP was diagnosed if an increase in β - hCG was detected following D&C. Also, EP was excluded or confirmed based on the presence or absence of chorionic villuses on histological examination respectively in women with decreasing levels after D&C.

Although the management strategy was the based on the choice of the attending gynecologist, priority was given to medical management with MTX in suitable women with un-ruptured EPs in our clinic as stated elsewhere[7-11]. Women were found eligible for treatment with MTX, if (1) they were hemodynamically stable, (2) had un-ruptured EP, (3) and / or EP size was < 5 cm, (4) and normal baseline hematological, hepatic and renal laboratory tests as evidenced by AST less than twice of upper limit of normal, serum creatinine < 1.2 mg/dl and platelet count > 100,000 / ml and white blood cell count > 4000 /ml. However, a spontaneously decreasing β - hCG levels was also considered a contraindication for any intervention and was managed expectantly unless a plateauing or rising levels were encountered during follow-up. Women managed expectantly were only included in analysis, if the diagnosis of EP was certain.

Single dose MTX protocol is the preferred medical treatment in stable consenting women in our clinic similar to protocols stated previosly[7-11]. Briefly, intramuscular MTX at a dose of 50 mg/m^2 of body surface area was given on day 1 and serum β - hCG level was checked on days 4 and 7. Women with decreasing serum β - hCG > 15% from day 4 to 7 were followed up weekly until it was < 15 mIU / ml. If there was < 15% decrease in serum β - hCG between day 4 and 7 or rising or plateauing levels on weekly follow-up, an additional dose of MTX was given with a maximum of three doses. Requirement of more than three doses or the need for surgery (*i.e.*, rupture, acute abdomen and excessive pelvic fluid collection) during follow up of MTX treatment was defined as treatment failure.

Women were referred for surgery in the presence of hemodynamic instability, suspicion of rupture, a considerable amount of fluid collection in pelvis and rejection of medical treatment by women. Decision to operate either with laparotomy or laparoscopy was based on the urgency of condition, experience and availability of equipment and surgical staff for laparoscopy and the preference of women. Treatment failure for surgery was defined as the requirement of an additional dose of MTX or repeat surgery (*i.e.*, persistent ectopic pregnancy).

In addition to demographic data, pre-treatment and post-treatment serum β - hCG levels, ectopic mass size, presence of fetal cardiac activity, pelvic fluid collection and time of resolution of β - hCG in days, number of MTX courses, number of women who needed an adjuvant MTX therapy or repeat surgery post-operatively were collected for analysis. The success of treatment modalities was compared.

The PASW statistics (SPSS version 18 Chicago, IL, USA) was used for analyses. Continuous variables were given as mean ± standard deviation; categorical variables were defined as percentages. Comparison of the groups was evaluated by using the chi-square test for categorical variables. In the comparison of more than two groups, the univariate variance analysis was used in variables with normal distribution (One way-ANOVA test), while the Post Hoc test (Tukey-HSD) was used as a secondary test in multiple comparisons. A p-value of < 0.05 was considered as significant.

RESULTS

Medical records of 124 women diagnosed with EP were found during the study period. Seven were excluded because of the incomplete records and another 11 were excluded because an aborting intrauterine pregnancy could not be excluded. Remaining 106 were found eligible for inclusion into analysis.

Demographic characteristics of women are presented in Table 1. The presenting symptom was vaginal bleeding in 18 (17%), abdominal pain in 17 (16%), acute abdomen in 22 (21%) and amenorrhea in 16 (15%) women. Only 40 (38%) women had visible

Table 1: Comparison of demographic characteristics, symptoms, ultrasonographic and hematologic parameters of women on admission between groups

Patient characteritics, symptoms and parameters	Expectant (21) Mean ± SD n (%)	Medical (46) Mean ± SD n (%)	Surgery (39) Mean ± SD n (%)	p-value
Age (years)	29.4 ± 6.1	29.7 ± 5.4	31.9 ± 4.5	0.099
Gestational age (days)	39.2 ±15.4	47.6 ± 22.3	37.2 ± 13.5	0.042 $p^3 = 0.046$
Gravidity	2.9 ± 1.4	2.9 ± 1.4	2.9 ± 1.4	0.048 $p^3 = 0.038$
Parity (N = 76)	1.1 ± 1.2	1.2 ± 1.0	1.6 ± 1.2	0.158
Previous abortion (N = 27)	0.6 ± 0.8	0.2 ± 0.6	0.5 ± 0.9	0.074
Previous curettage (N = 14)	5 (19)	5 (11)	4 (10)	0.589
Previous ectopic (N =2)	1 (4.8)	-	1 (2.6)	0.383
Vaginal bleeding	7 (35)	17 (37)	5 (13)	0.039 $p^2 = 0.035$ $p^3 = 0.030$
Abdominal pain	3 (14)	5 (11)	10 (25.6)	0.183
Acute abdomen (N = 22)	-	4 (9)	18 (46)	< 0.001
Amenorrheic	-	11 (24)	5 (13)	0.035
Visible ectopic mass by ultrasonography	6 (29)	22 (48)	12 (31)	0.170
Embryo with a heart beat	-	2 (4)	4 (10)	0.229
Ectopic mass diameter (mm)	16.8 ±11.4	17 ± 6.6	30 ±15.6	0.007 $p^3 = 0.007$
Hemoglobin (g/dl)	12.4 ± 1.2	12.1 ± 1.3	11.5 ± 1.7	0.029 $p^2 = 0.043$

Mean ± SD: Mean ± standard deviation, n (%): number (percentage), p^1: expectant vs medical, p^2: expectant vs surgery, p^3: medical vs surgery

ectopic mass with mean a diameter of 21 ± 12 mm and six (5.6 %) women had an embryo with a heartbeat at transvaginal ultrasonography.

Twenty-one women were primarily managed expectantly and it was succesful in 66.7% (14/21) patients. Three women required medical treatment and four required surgery due to plateauing or rising β-hCG levels during follow-up (Table 2). Two women were treated with salpingostomy and two others with salpingectomy.

A total of 49 women were treated with MTX including three women with failed expectant management. Medical management was the primary mode of treatment in 46 (43.4%) women with only three (3%) receiving a multi-dose regimen (Table 2). Among the 43 women who received single dose MTX as primary treatment 79% (34/43) were successful. The cumulative success rate of medical management group increased to 81.6% (40/49) when three women who received it as secondary mode of treatment were taken into consideration in addition to other three women who received multidose MTX treatment. Nine women were considered unsuccessful for medical treatment with MTX because two women needed more than three doses of MTX and seven women required surgery following MTX for rupture (4 women) and tubal abortus (3 women) causing hemodynamic instability. Among those requiring surgery, three women were treated with laparoscopic salpingostomy and four others had salpingectomy with laparotomy, all successfully.

Surgery was the primary treatment modality in 39 (36.7%) women; 18 (46 %) were managed with laparoscopy and 21 (54 %) with laparotomy (Table 2). Among those in whom surgery was the primary modality, salpingostomy was done in 18; and salpingectomy was performed in 21 patients, nine of them for tubal rupture. Salpingostomy was done with laparoscopy in 13 (78%), and with laparotomy in five (22%) women. Additionally, secondary surgery was performed for 11 (10.3%) women in the whole cohort with four (36%) who failed expectant management and seven (64%) patients who failed MTX treatment taking the total number of women who were treated with surgery to 50 (23 salpingostomies and 27 salpingectomies). Laparoscopic salpingostomy was successful in 12 (92.3%) women, but failed in one (7.7%) who had a pre-treatment β-hCG of 8562 mIU/ml with a visible fetal heart beat, and she was treated with a single dose of postoperative MTX successfully.

When treatment groups were compared; salpingectomy was more successful compared to expectant and medical managements (100% Vs 66.7% for salpingectomy Vs expectant management respectively, p = 0.003; and 100% Vs 79% for salpingectomy and medical management respectively, p = 0.040, Table 2). Likewise, the success rate of salpingostomy was higher than expectant

Table 2: Treatment modalities and success rates between groups

Treatment modalities	Expectant n (%)	Medical n (%)	Salpingostomy n (%)	Salpingectomy n (%)	p-value
Primary intervention	21	46	18	21	
Medical therapy requirment	3		1		
Surgery requirment	4	7			$p^1 = 0.063$
Success rate	14 (66.7)	34 (79)	17 (94.4)	21 (100)	$p^2 = 0.246$ $p^3 = 0.003$ $p^4 = 0.040$
Cumulative success rate	14 (66.7)	40(81.6)	22 (95.7)	27 (100)	

p^1 = expectant management vs laparoscopic salpingostomy, p^2 = medical treatment vs laparoscopic salpingostomy, p^3 = expectant management vs salpingectomy, p^4 = medical treatment vs salpingectomy

management; 94.4% Vs 66.7% respectively, but this did not reach statistical signifigance (p = 0.063). Similarly, when conservative interventions are compared, the success of salpingostomy and medical management did not differ statistically (79% and 94.4%, respectively, p = 0.246). Additionally, the cumulative success rates were 81.6%, 95.7%, and 100% in medical management, salpingostomy, and salpingectomy groups, respectively.

Initial β-hCG levels were significantly higher in surgery group than expectant and medical groups: 3276 ± 2761 mIU/ml, 1023 ± 674 mIU/m and 1844 ± 2025 mIU/m, respectively (p-value for expectant Vs surgery < 0.001; p-value for medical Vs surgery = 0.004, Table 3). Mean time to resolution of β-hCG in expectant, medical and surgery groups was 26 ± 16, 35 ± 22 and 18 ± 9 days, respectively with a significance only between medical and surgery groups (p < 0.001).

DISCUSSION

To date, there are mainly three therapeutic options for EP; expectant, medical and surgical treatment. Expectant management is acceptable only for hemodynamically stable women presenting with low initial β-hCG (< 1000 mIU/ml) levels and / or levels that are spontaneously decreasing[10,11]. Elson *et al* reported 70% success rate with expectant management in their study including 107 women with EP[12]. They found 96% success rate when initial ß-hCG was ≤ 175 IU/ml and 21% when initial ß-hCG was ≥ 1500 IU/ml. In the present study, we found 67% success rate for expectant management for a mean ß-hCG value of 713 IU/ml. This success rate is in accordance with the classical view that expectant management should be considered when ß-hCG ≤ 1000. However, we should anecdotally note that we noticed many women managed successfully with expectant management when initial ß-hCG was ≥ 1000 IU/ml, and also cases presenting with rupture despite initial ß-hCG ≤1000 IU/ml and spontaneously decreasing titer during expectant management. So, one should never rely completely on initial ß-hCG value and decreasing titers during expectant management and should follow-up women cautiously and patiently till ß-hCG decreases ≤ 15 IU/ml.

The medical treatment with MTX using either multi- or single dose protocol has been adopted into armamentarium in last few decades and has the advantage of avoiding of risks of surgery and anesthesia, high efficacy, simplicity, cost-effectiveness[13,14]. Although the success rates between the two protocols are debatable, most agree on equal or slightly higher treatment efficacy of multi-dose protocol[15]. However, it cannot offset the other indirect advantages of single dose protocol which is in fact the most favoured one due to shorter hospital stay, fewer

Table 3. Comparison of level and resolution time of β-hCG between groups

Level and resolution time	Expectant (21) Mean ± SD	Medical (46) Mean ± SD	Surgery (39) Mean ± SD	p-value
β-hCG level on 1st day (mIU/ml)	1023 ± 674	1844 ± 2025	3276 ± 2761	$p^1 = 0.226$ $p^2 < 0.001$ $p^3 = 0.004$
β-hCG resolution time (days)	26 ± 16	35 ± 22	18 ± 9	$p^1 = 0.098$ $p^2 = 0.243$ $p^3 < 0.001$

Mean ± SD = Mean ± Standard Deviation, p^1 = expectant vs medical, p^2 = expectant vs surgery, p^3 = medical vs surgery, Post hoc Tukey test was used

office visits, low cost and fewer side effects[16]. We favour single dose regimen in our clinic. Only three women with EP were treated with multi-dose regimen and all were successful. Therefore, we could not make a comparison with single dose regimen because of the low number of cases.

Usually, the decision to perform surgery with either laparoscopy or laparotomy is straightforward in an emergency. But laparoscopic salpingostomy became the standard contemporary surgical approach for women desiring future fertility with un-ruptured EP[17]. However, the most convenient primary treatment for women who wishes to preserve future fertility is debatable between medical treatment and surgery in un-ruptured EP, specifically between the single dose methotrexate and laparoscopic salpingostomy. Only few studies have directly compared the single dose methotrexate with laparoscopic salpingostomy with contradictory results so far. In a prospective randomized study by Hajenius *et al* involving 100 women, treatment was successful in 82% (42/51) and 72% (35/49) after systemic single dose MTX and laparoscopic salpingostomy respectively with comparable success and tubal patency rates[18]. Only two (4%) women needed a second dose of MTX in this study. In another trial with similar design involving 75 women with EP, both treatments had similar success with a slightly insignificant superiority of systemic single dose medical treatment; 94.7% (36/38) Vs 91.4% (33/36) with 15% of women in MTX group receiving more than one dose[7]. However, both these studies used MTX in a dose of 1 mg/kg, which is actually a lighter dose in contrast to usual standard dose of intramuscular 50 mg/m^2 used in current single dose MTX protocols. Recently, Moeller *et al* confirmed similar results in a prospective study with 106 women[19]. Statistically, similar success rates with single dose MTX and surgery (74% and 87%, respectively) were found in addition to the subsequent spontaneous intrauterine pregnancy rate of 73% after MTX and 62% after surgery; and the EP rate was 9.6% after MTX and 17.3% following surgery. However, Sowter *et al* found that the single dose systemic MTX is less effective than laparoscopic salpingostomy in a prospective study with 62 women (65% Vs 93%) and concluded that it should only be offered as an alternative to surgery to women who have mild symptoms and present at low serum β-hCG concentrations[20].

All these studies, including ours, were handicapped with small sample size. Additionally, studies differed in the number of women who needed additional doses of MTX and the inclusion criteria for MTX treatment with respect to the pre-treatment serum β-hCG levels, ectopic mass size, presence of fetal cardiac activity, all potentially affecting the success rates of treatment modalities. But a comprehensive meta-analysis consisting of four randomized prospective studies with a total of 265 women has concluded that the systemic single dose MTX was significantly less successful than laparoscopic salpingostomy when only one injection was considered as single dose (RR 0.82, 95% CI 0.72 – 0.94)[20]. However, among the 120 women treated with systemic single dose MTX, cumulative success rates after one, two, three and four 'single dose' were increased to 77, 92, 93 and 94% respectively with no difference with laparoscopic salpingostomy (RR 1.01, 95% CI 0.92 – 1.12).

In our study, we accepted the need for a second or third dose of MTX as a failure in our single dose MTX group. Despite this, the success rate of single dose MTX was 79%, comparable to that of salpingostomy, which had a success rate of 92.3% with non-significant difference between the two modalities. We believe that if we had accepted the success of single dose regimen after the inclusion of a second and / or third dose in case of failure of first injection, our success rate would be higher and closer to that of laparoscopic salpingostomy. We think that our high success rate in both modalities results from appropriate patient selection, strict adherence to treatment guidelines of EP and our experience in laparoscopic surgery. In another retrospective analysis conducted in our clinic between 2002 and 2006 with 60 women, expectant, single dose and surgery was the primary mode of treatment in 23%, 20% and 53% of cases respectively[21]. Our success rate for single dose MTX was 77%. In the present study, single dose MTX and surgical management were the primary modes of treatments in 43% and 39% of women respectively which shows that treatment of choice was shifted from surgery to medical management in the last five years compared to the previous five-year period. However, there was only a very slight improvement in the success rate of single dose MTX between two periods (77% Vs 79%). This may have resulted from enthusiasm in managing some EPs with MTX in the last five years that were previously considered as too advanced to be treated with medical therapy and hence, were treated surgically.

Results with systemic MTX are comparable to the outcomes of laparoscopic salpingostomy for EP in terms of persistent trophoblastic tissue, tubal patency and future fertility[22,23]. However, longer time is needed for the decrement of β-hCG below 15 mIU/ml than with laparoscopic salpingostomy. Decrease in the efficacy and cost effectiveness at higher pre-treatment β-hCG levels, presence of EP mass > 4 cm, fetal cardiac activity, decrease in health related quality of life during treatment and the possibility of an emergency surgery for failed treatment are the drawbacks of systemic MTX treatment[11,24].

CONCLUSION

The highest success rate in EP is achieved by surgical treatment. However, expectant and medical treatment may eliminate the need for surgery in selected cases that have low and decreasing initial β-hCG levels. Salpingostomy and single dose MTX seem to have comparable results, but both have their own advantages and disadvantages. Desire of patient, caretaker's experience and facilities of the settings are other factors that should be taken into account in determining the treatment modality.

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Case Report

Malignant Granular Cell Tumor Manifesting as Exophytic Skin Lesion: Report of a Case

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ABSTRACT

Granular cell tumor (GCT) also known as Abrikossoff tumor is an uncommon tumor of putative Schwannian derivation that is rarely malignant. We report a case of malignant granular cell tumor (MGCT), which manifested as an ulcerated exophytic skin lesion. The patient was a 41-year-old male who presented with a progressively enlarging, ulcerated skin lesion of six month duration, in the left inguinal region. On examination a well-circumscribed elevated and ulcerated lesion was identified. The lesion was firm in consistency and was fixed to the skin. A clinical diagnosis of squamous cell carcinoma was considered. The lesion was excised with wide surgical margins. Microscopic examination revealed solid sheets of polygonal to spindle cells with moderate pleomorphism. Most cells revealed prominent nucleoli and mitosis was frequent. The cells were strongly immunoreactive to S100, vimentin and neuron-specific enolase. The tumor cells expressed p53 and Ki-67 in about 60% and 40% of the cell population respectively. A diagnosis of MGCT was made. We report this case because of its unusual clinical presentation and briefly discuss its prognosis and differential diagnosis.

KEY WORDS: Granular cell tumor, immunohistochemistry

INTRODUCTION

Granular cell tumor (GCT) is an uncommon lesion. It was first described in 1926 by AbriKossoff who postulated a myogenic origin and coined the term 'granular cell myoblastoma'[1]. In 1962, Fisher and Wechsler suggested the concept of neural differentiation based on the presence of an incomplete basal lamina and numerous intracellular, membrane-bound autophagic vacuoles that contain myelin figures in addition to other cellular debris[2]. Cytogenetic analysis demonstrated that 60% of cultured tumor cells display the following karyotype 46,XX, + X,dic(5;15)[3]. The tumor typically presents as a slow growing, solitary and painless nodular lesion located on the skin, on the tongue and other parts of the body[4]. It can affect people of any age, race or sex, although it is more prevalent between the 4th to 6th decades of life with a predilection for females[3]. Fewer than 2% of all GCT are malignant[5]. Malignant granular cell tumor (MGCT), first described by Ravich *et al* [6] in 1945, arose from the urinary bladder of a 31-year-old woman. The tumor is an extremely rare, high grade sarcoma with a high rate of metastases and poor prognosis. We herein present a case of MGCT with gross, light microscopic and immunohistochemical findings and briefly discuss its prognosis and differential diagnosis.

CASE REPORT

A 41-year-old male presented with complaints of swelling in the left inguinal region of six-month duration. On examination, a firm, non-tender, ulcerated, exophytic skin lesion measuring about 4.5 cm in diameter was identified. The lesion was firm with restricted mobility and fixed on the skin. There was no associated regional lymphadenopathy. Laboratory investigations were non-contributory. The patient underwent wide local excisional biopsy of the lesion due to the clinical suspicion of squamous cell carcinoma. At surgery a firm, well-circumscribed, fungating elevated lesion with extension into the subcutaneous tissue was identified. His postoperative period was uneventful and he was discharged on postoperative day seven.

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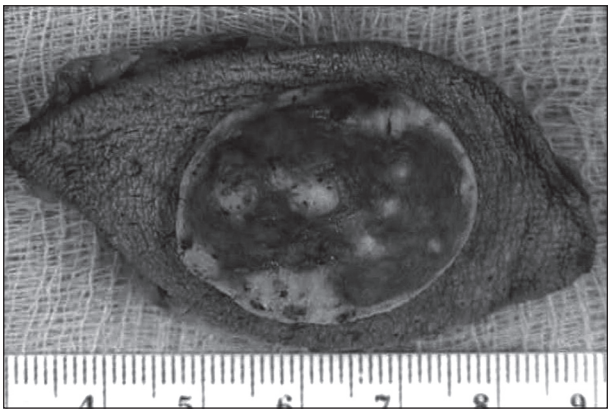

Fig. 1: Gross photograph of the MGCT exhibiting an exophytic and ulcerated skin lesion

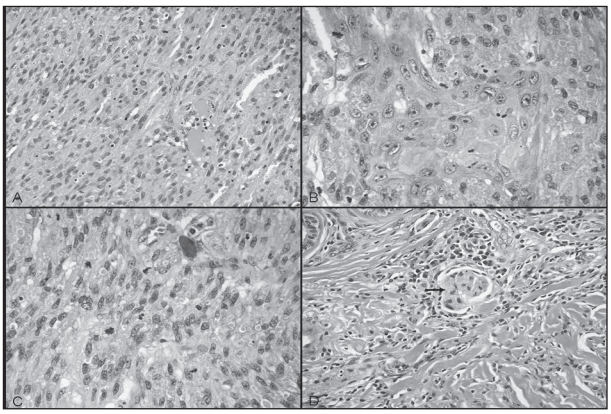

Fig. 2: Photomicrograph of the MGCT exhibiting (A) the spindle cells in sheets and running in fascicles with moderate pleomorphic nuclei (H&E X100). (B) Most of the cells have prominent nucleoli (H&E X400) with (C) frequent mitosis (H&E X400) and (D) An occasional focus of lymphatic invasion (arrow) noted (H&E X400)

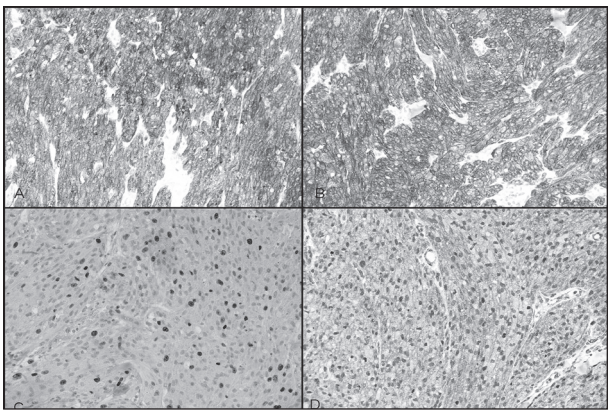

Fig. 3: Photomicrograph of the immunohistochemistry showing reactivity to (A) S100 and (B) NSE. The tumor shows (C) Ki-67 positivity in about 40% of the tumor cells and (D) p53 expression, in greater than 60% of the cell population (Avidin biotin peroxidase X200)

Gross and Microscopic examination

We received a well circumscribed, fungating and elevated skin lesion measuring about 4.5 x 4.5 x 4.3 cm (Fig. 1). The elevated surface was ulcerated. The cut section of the mass was homogenous, grey white, firm in consistency with extension into the subcutaneous fat. Microscopic examination revealed solid sheets of tumor cells in the dermis (Fig. 2A). The tumor cells were infiltrating the dermal collagen and reaching the subcutaneous fibroadipose tissue. The tumor cells displayed a polygonal to spindle shaped nuclei with pale eosinophilic granular cytoplasm. The nuclei were vesicular and demonstrated moderate pleomorphism. Most of them had prominent nucleoli (Fig. 2B). Mitosis was frequent (8 per 10 HPF) (Fig. 2C). No necrosis was observed. PAS positive, diastase resistant intracytoplasmic granules were present in most of the tumor cells. Occasional foci of lymphatic invasion were noted (Fig. 2D). Overlying epidermis was ulcerated and exhibited extensive pseudoepitheliomatous hyperplasia at the periphery of the lesion. The deep resected plain and peripheral resected margins were free of the tumor. The cells were immunoreactive to S100 (Fig. 3A), vimentin, neuron specific enolase (NSE) (Fig. 3B), alpha-1-antitripsin and CD68; however they were negative for cytokeratin, smooth muscle actin (SMA), desmin, CD34, Melan A and HMB45. Ki-67 (Fig. 3C) was positive in about 40% of the tumor cells while p53 (Fig. 3D) expression was seen in greater than 60% of the cell population. Thus a diagnosis of MGCT was made.

The postoperative magnetic resonance imaging (MRI) and bone scan revealed no evidence of metastases. The patient received radiotherapy in a specialized center. He is now on follow-up for the last eight months and is free of the disease.

DISCUSSION

GCT is a benign rare tumor. A malignant course is encountered in about 2% of the cases. Skin and subcutaneous tissue is rare site for MGCT[7]. Torrijos-Aguilar *et al*[7] reported MGCT in a single patient in the cheek, in a series of 34 cases of cutaneous GCT. Some authors addressed that although morphology could not reliably predict the biological behaviour of GCTs, location at deep plane, local recurrence, rapid growth to a size greater than 4 cm and infiltrating pattern of growth should raised concerns about the possibility of malignancy[8,9]. Differentiation between benign GCT and MGCT is often difficult, and only the development of metastasis may establish the malignancy[10]. Since MGCT are extremely rare tumors, based on the cumulative experience of previous case reports, Fanburg-Smith *et al*[10] put forward six histologic criteria to be potentially important. These

include necrosis, spindling of the tumor cells, vesicular nuclei with large nucleoli, increased mitotic rate (> 2 mitosis/10 HPF), high nuclear to cytoplasm (N:C) ratio and pleomorphism. Histologically, MGCT is diagnosed when three or more of the criteria are fulfilled. If the neoplasm meets one or two criteria, it is classified as atypical GCT. If the tumor has none of the criteria or only focal pleomorphism, it is regarded as benign[10]. Although there was no evidence of metastases in this patient, the present case fulfilled four criteria out of the six, and was categorized as MGCT.

In addition to the morphologic features, upregulation of p53 as well as Ki-67, a nuclear proliferative marker, has been found to correlate with an aggressive clinical course and malignant behavior. In the recent study, p53 immunostaining was negative in all the benign cases, while p53 expression was seen in greater than 50% of the cell population in about 22% of the atypical GCTs and 68% of the MGCTs[10]. Similarly, benign GCTs exhibited Ki-67 in 1% or less of the tumor cell population while atypical GCTs and MGCT showed Ki-67 immunoreactivity in about 15% and 30% of the tumor cell population respectively[10]. Our current case documented expression of p53 and Ki-67 in about 60% and 40% of the tumor cells, respectively.

Aksoy *et al*[11], in a review of 35 cases of metastatic GCTs documented that most metastases develop within two years following diagnosis. Median disease free survival was about 17 months. Most of the affected sites were the lungs, liver and bones. The majority of these metastases were associated with local recurrence. Median overall survival from diagnosis was 84 months and median overall survival after the detection of metastases was 44 months. So patients who undergo surgical resection for GCT should be on close follow-up if unfavorable histological features are present[11].

There are various benign and malignant lesions which display granular cell features, and therefore, should be considered in the differential diagnosis of granular cell tumor. They include granular cell features in carcinoma, ameloblastic lesions, leiomyoma, leiomyosarcoma, dermatofibroma, dermatofibrosarcoma protuberans, malignant schwannoma, angiosarcoma and melanoma. Panel of antibodies including epithelial, smooth muscle, melanocytic and vascular markers are particularly useful when the granular cell features are diffuse and obscure the underlying lesion.

In the present case, the tumor was negative for cytokeratin, SMA, desmin, CD34 and melanocytic markers like HMB45 and Melan A and excluded the possible differential diagnoses mentioned above. Schwannomas and neurofibromas are S100 positive and may show granular changes in parts, although the changes are never extensive enough to create a major diagnostic challenge. Moreover, schwannomas are encapsulated, and other stigmata of von Recklinghausen disease associated with neurofibromas are absent in granular cell tumors. Although ultrastructural study was not undertaken in the present case, such studies might play an important role in excluding lesions that mimic true granular cell tumor. Identification of tonofilaments, well formed desmosomes, condensation of thin filaments of actin type, pinocytotic vesicles, Weibel-Palade bodies, and melanosomes are all features that indicate another neoplasm rather than true granular cell tumor.

Another close differential diagnosis of the present case, in particular, is primitive polypoid granular cell tumor first described by LeBoit *et al*[12]. This is a rare subset of GCT which present as exophytic skin lesion at various parts of the body in patients of any age. The lesion is cellular, spindled and often shows nuclear plemorphism with frequent mitosis. Immunohistochemically Lerman *et al* described diffuse and strong positivity for CD63 and vimentin, focally staining for SMA and CD68 and negative for S100 and NSE[13]. Our case illustrated strong positivity for S100 and NSE and therefore ruled out this lesion.

CONCLUSION

The diagnosis of the MGCT is crucial. The association of histological and clinical aspect to the immunoprofile is essential to establish the correct diagnosis of the lesion.

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Case Report

Late Onset Takayasu Arteritis: A Case Report and Literature Review

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ABSTRACT

Takayasu arteritis (TA) is a chronic inflammatory disease of the aorta and its major branches. It most often affects young women in the second and third decades of life.TA has been reported in children as young as six-month-old to adults of all ages. The initial complaints may be non-specific constitutional symptoms (*e.g.*, fever, weight loss, lethargy). Because these complaints lack specificity, the correct diagnosis may be delayed for months or years.There have been reported cases of TA associated with other auto-immune diseases as well as cases of atypical initial localizations (*e.g.*, pulmonary) which had a late onset of disease. We present a case of TA in a 52-year-old Srilankan woman referred from the polyclinic with a chief complaint of headache of three months duration and arthralgia of 15-year duration.

KEY WORDS: large vessel vasculitis, Takayasu arteritis

INTRODUCTION

Takayasu arteritis (TA) is a large vessel arteritis primarily affecting the aorta and its major branches. The inflammation may be localized to a portion of the thoracic or abdominal aorta and branches, or may involve the entire vessel. It is a chronic type of vasculitis of unknown etiology. Women are affected in 80 to 90 percent of cases, with an age of onset that is usually between 10 and 40 years. It has a worldwide distribution, with the greatest prevalence in Asians. HLA-BW52 and HLA-B39 are increased in frequency in several studies, suggesting an immunogenic association[1].

Despite the term pulseless disease, which is a synonym for TA, the predominant finding in individuals with TA is asymmetric pulse. Absent peripheral pulses occur late in the course of the disease. Although 5-year survival rates exceed 90%, the disease has a high incidence of residual morbidity

CASE REPORT

A 52-year-old Srilankan female with no past medical history was referred from a polyclinic for headache of three months duration. The headache was left hemicranial, continuous, of modest severity with no associated vomiting, loss of consciousness or seizures. There was no history of fever, weight loss, joint swelling, visual symptoms or skin rash.Systemic review was unremarkable except for knee and ankle joint arthralgia with generalized body aches, on and off over 15 years duration.

She was married and had three grownup children and was still menstruating.

On general examination, she looked well, afebrile with a pulse rate of 90/min.The radial, brachial, carotid and superficial temporal pulses over the right side were not palpable. She had a significant right carotid bruit. Other pulses were felt equally with normal volume. Her blood pressure in the right upper limb was 90 / 70 mmHg and in the left upper limb was 150 / 70 mmHg with no orthostatic changes. Systemic examination was unremarkable with no significant cardiac murmurs and fundoscopy was normal.

Her initial erythrocyte sedimentation rate (ESR) was 69 mm / hr. The results of the rest of her laboratory investigations are shown in Table 1. Magnetic resonance angiography (MRA) for the arch of the aorta and neck vessels revealed significant narrowing of the right innominate artery and proximal right subclavian and common carotid arteries. The luminal caliber

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Table 1: Laboratory investigation results

Laboratory test	Value	Normal range
White blood cell (WBC)	9.1	3.9 – 11.1 10^9/l
Hemoglobin (HB)	10.2	11.8 – 14.8 g /l
Mean corpuscular volume (MCV)	74	82 – 98 fl
Platelets count (PLT)	439	150 – 400 10^9/l
Erythrocyte sedimentation rate (ESR)	69	< 20
Prothrombin time (PT)	12.6	10.5 – 12.5 seconds
Activated partial prothrombin time (APTT)	27.5	25 – 38 seconds
Glucose (random)	7.2	6.7 – 11.1 mmol/l
Creatinine	51	40 – 90 μmmol / l
Blood urea nitrogen (BUN)	3.6	2.5 – 6.6 mmol/l
Albumin	31.9	35 – 48 g/l
Total protein	79	64 – 83 g / l
Alkaline phosphatase	91	53 – 141 u/l
Alanine transferase (ALT)	13	10 – 60 u/l
Aspartate tranferase (AST)	18	10 – 40 u/l
Gamma glutamyle transferase (GGT)	18	9 – 40 u / l
Sodium (Na)	137	136 – 146 mmol / l
Potassium (K)	4.2	3.5 – 5.2 mmol / l
Corrected calcium	2.6	2.2 – 2.6 mmol / l
Antinuclear antibody (ANA)	Negative	
Antidouble stranded DNA	Negative	
Cytoplasmic antinutrophil- cytoplasmic antibody (c-ANCA)	Negative	
Perinuclear antinutrophil- lcytoplasmic antibody (p-ANCA)	Negative	< 20
Rheumatoid factor (RF)	Negative	

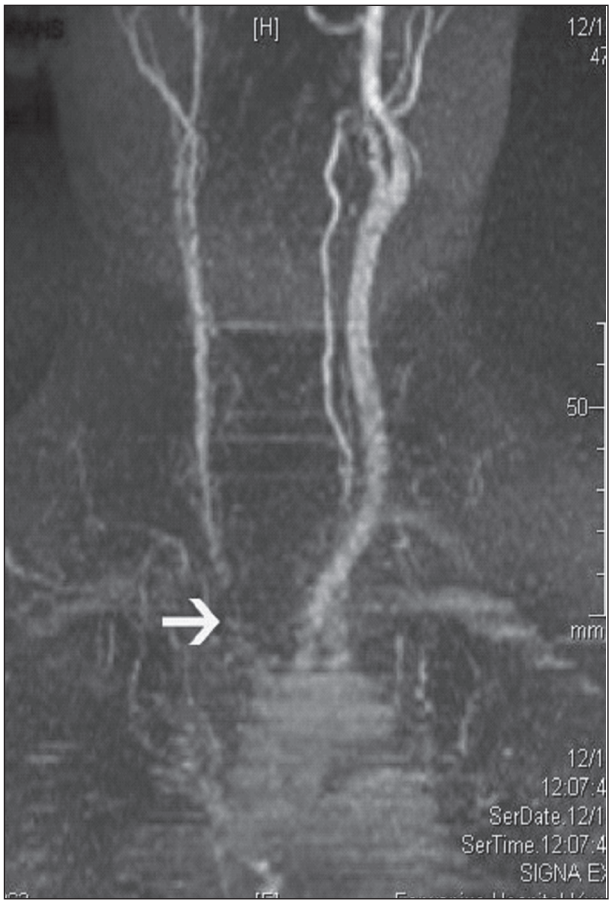

Fig. 1: Magnetic resonance angiography (MRA) for the arch of the aorta and neck vessels showing significant narrowing of the right innominate artery and proximal right subclavian and common carotid arteries (arrow). The luminal caliber of the rest of the distal right common, internal and external carotid arteries was also significantly reduced as compared with the left carotid vessels.

of the rest of the distal right common, internal and external carotid arteries was also significantly reduced as compared with the left carotid vessels (Fig. 1). The right vertebral artery was not visualized in its entire course (Fig. 2). The left vertebral artery was normal. The arch of the aorta, left common carotid and left subclavian arteries appeared normal.

The diagnosis of TA was made based on clinical, laboratory and radiological findings and the patient was started on oral prednisolone at a dose of 1 mg/kg/day, based on the recommendations of the rheumatology service. The patient improved dramatically regarding her symptoms and her ESR dropped to 20 mm/hr. On subsequent follow-up visits to the outpatient department, her pulses on the right upper limb were weak but palpable. She was started on weekly methotrexate therapy at a dose of 15 mg and folic acid aiming at tapering the dose of prednisolone as far as tolerated.

DISCUSSION

TA is characterized by granulomatous inflammation of the aorta and its major branches, leading to stenosis, thrombosis, and aneurysm formation. Stenoses are found in 90% of patients with TA. Patients often have post-stenotic dilatations of the arteries. Symptoms of vascular compromise may be minimized by the development of collateral circulation with the slow progression of stenosis. Vessel wall dissection or aneurysm may occur in areas weakened by inflammation[2, 3]. In 1990, the American College of Rheumatology suggested a set of criteria for the diagnosis of TA. The criteria consist of: (a) age < 40 years, (b) claudication of an extremity, (c) decreased brachial artery pulse, (d) > 10 mmHg difference in systolic pressure between the left and right arm, (e) a bruit over subclavian arteries or aorta and (f) angiographic evidence of narrowing or occlusion of the aorta or its primary or proximal branches. Presence of three out of the six criteria is required for the diagnosis[4]. TA is rarely associated with other autoimmune diseases, such as systemic lupus erythematous (SLE) and systemic sclerosis (SS). There have been reported cases of late onset TA with

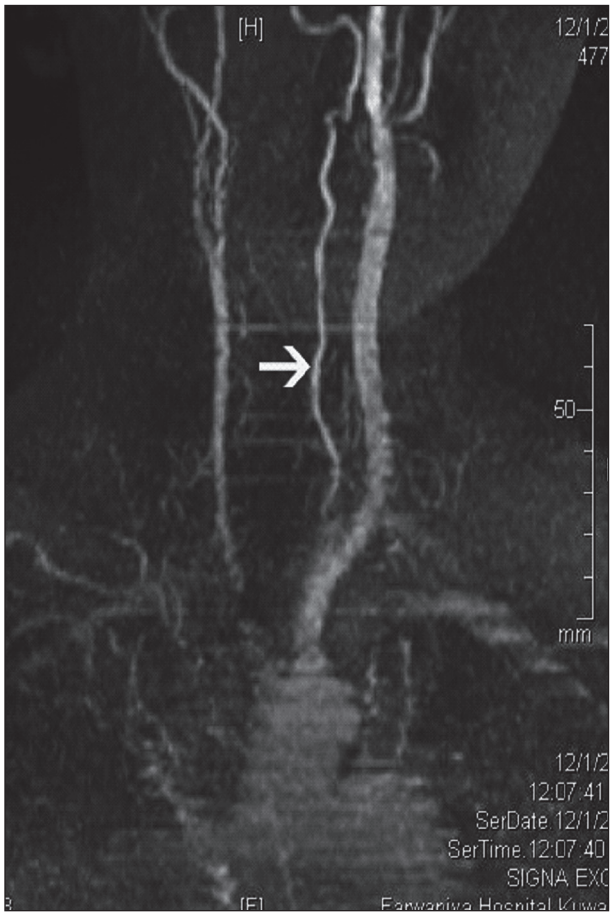

Fig. 2: The right vertebral artery was not visualized on its entire course. The left vertebral artery was normal (arrow).

arthritic manifestations in Japan[5]. Our patient is one of several cases developing TA after arthritic signs and symptoms. Nakabayashi *et al* found 20 other cases of rheumatoid arthritis (RA) associated with TA in the English literature[5]. These were composed of 14 female and six male patients, with a mean age of 48 ± 14.6 yr (range 16 – 74 years) at the time of diagnosis of RA. The mean age at the time of diagnosis of TA was 55.5 ± 15 yr (range 20 – 82 years), which was higher than isolated TA. The average time elapsing between the onset of RA and the development of TA was 7.5 years. Twelve cases were not diagnosed until autopsy. The death of seven out of these patients was directly attributed to vasculitis.

A study of 107 cases of TA, the aim of which was to correlate RA and TA, found that whilst there was a weakly positive rheumatoid factor (RF) in some patients with arthralgia, there was no correlation between the presence of arthritis and a positive RF[6]. Likewise, in a study of 84 patients with TA, 12 had a history of arthralgia. Only one out of them had frank synovitis with a positive RF[7]. On the other hand, in a study of 32 North-American patients with TA, arthralgia and synovitis were present in 56% and 22% of patients respectively[8]. Sato *et al* from Brazil showed that arthralgia or arthritis were present in 26% of patients with TA[9]. Such a clinical difference regarding arthritis and arthralgia in the course of TA may be attributable to a genetic background, as polymorphic HLA genes and their combinations may have a role in modulating the clinical findings.

Inflammation of the small and medium-sized arteries in the extremities may be seen in RA. Aortitis and aortic root changes were previously reported in patients with RA. Although clinically evident aortic incompetence is rarely seen in patients with RA during their lifetime, necropsy data suggested that aortitis and aortic valvulitis may be seen in up to 15% of cases. RA that causes aortitis is almost always a severe, seropositive and nodular disease, associated with extra-articular vasculitic manifestations.

The medium age of patients with pulmonary manifestations as initial localization of TA appears to be higher[10]. Therefore, the diagnostic criteria for TA should be adapted accordingly and the age criterion could be abandoned in certain situations especially in patients with atypical manifestations (*e.g.*, arthritic, pulmonary) or those associated with other autoimmune diseases. To determine whether our patient will develop other autoimmune disease in the course of her illness, she needs to be closely followed up clinically and by serology.

CONCLUSION

The correct diagnosis of TA may be delayed for months or years because of the non-specific initial symptoms and signs. Proper history and meticulous physical examination especially for pulses and blood pressure recording in both upper limbs is mandatory. Furthermore, TA is rarely associated with other autoimmune diseases. Our patient is one of those unusual cases developing TA after arthritic symptoms. Such cases are noticed to have an older age of onset.

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Case Report

Infantile Nephropathic Cystinosis: Case Series and Review of Literature

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ABSTRACT

Cystinosis is a rare metabolic disease with an autosomal recessive inheritance. It is characterized by deposition of an extraordinary amount of cystine in different organs of the body.
Children with infantile nephropathic cystinosis (INC) present with failure to thrive, polyuria, polydipsia and photophobia in early infancy. They progress to chronic renal failure (CRF) between the ages 5 to 10 years. The diagnosis of cystinosis should be considered in young children with failure to thrive or CRF of unknown etiology. Cysteamine is effective in delaying the progression of this disease.
Four patients with INC from two families were followed over the last few years. All of them presented with polyuria, polydipsia, failure to thrive and rickets. Laboratory findings included glucosuria, hypophosphatemia, hypokalemia, proteinuria and later on azotemia. Therapy with cysteamine showed clinical improvement when started early.

KEY WORDS: chronic renal failure, cysteamine therapy, cystinosis

INTRODUCTION

Cystinosis is the major cause of inherited Fanconi syndrome, and should be suspected in young children with failure to thrive and signs of renal proximal tubular damage. Infantile nephropathic cystinosis (INC) involves many organs and systems particularly, kidneys which are the first to get involved leading to renal insufficiency

The diagnosis can be missed in infants, because not all signs of renal Fanconi syndrome are present during the first months of life. Measuring elevated white blood cell cystine content is the cornerstone for making the diagnosis[1].

The diagnosis is confirmed by molecular analysis of the cystinosine gene. Corneal cystine crystals are invariably present in all patients with cystinosis after the age of one year. Treatment with the cystine depleting drug cysteamine should be initiated as soon as possible and continued lifelong to prolong renal function survival and protect extra-renal organs[2].

CASE HISTORIES

Case 1:

A five-year and eight-month-old non-Kuwaiti girl presented at the age of seven months with polyuria, polydipsia and failure to thrive. She was the 3rd child of consanguineous parents. There was no significant family history other than type II diabetes mellitus. She was below the 3rd centile for height and weight and had evidence of rickets on clinical examination. Initial investigations showed the following: hemoglobin 9 g/dl, MCV 70fl, RDW 18%, WBC 11.4 x 10^9/l, platelets 300 x 10^9/l, Na 135 mmol/l, potassium 2.5 mmol/l, chloride 110 mmol/l, bicarbonate 10 mmol/l, albumin 35 g/l, ALP 850 IU/ml, calcium 2.36 mmol/l, phosphate 0.43 mmol/l, urea 3.6 mmol/l, creatinine 55 mmol/l, PTH 5.9 pmol/l (NR 1.3 - 8.5). Urine dipstick test revealed glucose + and protein + and fractional excretion of phosphate 70%. Urine amino acid chromatography showed marked generalized aminoaciduria. These findings were consistent with Fanconi syndrome. WBC cystine quantification was 3.9 nmol/1/2 cystine/mg protein. X-ray of hand and wrist showed changes of rickets. Cystine crystals were detected on slit lamp evaluation of the eye at age of 15 months. These results confirmed the diagnosis of cystinosis. She was commenced on phosphate, potassium, bicarbonate, and alphacalcidol supplements. At the age of two years, she was commenced on cystagon, initially on a dose of 2 – 3 mg/kg QDS. This was gradually increased

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weekly so as to reach a maintenance dose of 12.5 mg/kg QDS. However, the patient was non-compliant with cystagon therapy due to gastrointestinal upsets. Cystagon eye drops were also started.

At the age of three and half years, she was investigated for short stature. The following laboratory results were obtained: TSH 10 mIU/l, FT_4 14 pmol/l, IGF 15 nmol/l (NR10 – 66), GHl 13 mIU. She was commenced on eltroxin and growth hormone. Follow-up investigations showed deterioration of renal function: creatinine 150 umol/l, urea 10 mmol/l, phosphate 1.5 mmol/l, Ca^{++} 2.5 mmol/l, ALP 350 IU/l, bicarbonate 19 mmol/l, K^+ 3.8 mmol/l, WBC cystine 1.9 nmol/1/2 cystine/mg protein, TFT 2.5 and FT_4 22 pmol/l. Her weight and height were now on 3rd centile for age.

Case 2

The younger brother of case 1, one and half-year old presented at the age of eight months (after diagnosis of his sister) with polyuria, polydipsia and slight bowing of his legs. Investigations at this time revealed: creatinine 38 umol/l, bicarbonate 16 mmol/l, K^+ 3.2 mmol/l, phosphate 0.8 mmol/l, ALP 450 Iu/l, PTH 1.1 pmol/l, WBC cystine 2.7 nmol/1/2 cystine/mg protein. Urine analysis revealed glucose +, protein + and generalized aminoaciduria in a pattern typical of Fanconi syndrome. X-ray of hands and wrists showed evidence of rickets. There was no evidence of crystals on slit lamp examination of the eyes. He was commenced on phosphate, bicarbonate, potassium and alphacalcidol supplements.

At the age of 10 months, he was commenced on cystagon / 6h. Height and weight were maintained at 10th centile. The results at last follow-up showed K^+ 3.8 mmol/l, creatinine 55 umol/l, bicarbonate 20 mmol/l, phosphate 1.2 mmol/l, ALP 350 iu/l, WBC cystine 1.2 nmol/1/2 cystine/mg protein, TSH 2.6 mIU/l and FT_4 19 pmol/l. An ophthalmology review at the age of 13 months confirmed the picture of corneal crystal deposition. The child was started on cystagon eye drops.

Case 3 (2nd family)

A three and half-year-old non-Kuwaiti boy, 2nd issue of consanguineous parents, was noted to have polyuria, polydipsia and growth failure from 10th month of age. There was no significant family history other than hypertension. He was just below 3rd centile for height and weight and had clinical evidence of rickets. Initial investigations showed the following: Hb 10.5 g/l, MCV 78 fl, RDW 15%, Na^+ 136 mmol/l, K^+ 2.8 mmol/l, chloride 111 mmol/l, urea 3.1 nmol/l, creatinine 50 umol/l, phosphate 0.6 mmol/l, calcium 2.3 mmol/l, ALP 520 IU/l. Urine analysis showed protein +, glucose + and generalized aminoaciduria. WBC cystine was 3.5 nmol/1/2 cystine/mg protein. X-ray of hands and wrist showed changes of rickets. These results confirmed a diagnosis of cystinosis. Ocular slit-lamp examination showed no corneal deposits. He was commenced on phosphate, bicarbonate, potassium and alphacalcidol supplements. Cystagon was started at the age of 15 months. Insulin dependent diabetes mellitus was diagnosed at the age of 18 months and he was started on insulin therapy. At age of two years, laboratory investigations showed a TSH of 17mIU/l and FT_4 18 pmol/l. He was commenced on eltroxin replacement therapy. Investigations at last follow-up showed Na^+ 136 mmol/l, K^+ 3.8 mmol/l, phosphate 1.4 mmol/l, blood glucose between 10 - 12 mmol/l, creatinine 75 umol/l, WBC cystine 1.5 nmol/1/2 cystine/gm protein, TFT 4.1, FT_4 19. His weight and height were on 3rd centile for his age. Follow-up slit lamp examination showed corneal crystals and he was commenced on cystagon eye drops.

Table 1: Age of presentation, organs involved and complications

Case No.	Age at presentation (in months)	Organs involved	Complications
1	7	Kidneys	Fanconi syndrome
		Thyroid gland	Hypothyroidism
		Eyes (cornea)	Photophobia
		Pituitary gland	Short Stature
2	8	Kidneys	Fanconi syndrome
		Eyes (cornea)	Photophobia
3	10	Kidneys	Fanconi syndrome
		Thyroid gland	Hypothyroidism
		Eyes (cornea)	Photophobia
		Pancreas	Diabetes mellitus
4	9	Kidneys	Fanconi syndrome

Case 4 (2nd family)

The younger brother of case 3 presented at the age of eight months with polyuria, thirst, failure to thrive, vomiting and periods of dehydration. Initial investigations showed K^+ 2.6 mmol, phosphate 1.1 mmol, Na^+130 mmol, urea 8 mmol/l and creatinine 56 umol, pH 7.5, bicarbonate 25 mmol/l, chloride 90 mmol/l. These biochemical changes can mimic Barter syndrome. Urine showed glucosuria and amino-aciduria. WBC cystine was high at 5.7 nmol/1/2 cystine/mg protein confirming diagnosis of cystinosis. Slit-lamp examination was normal. He was commenced on K^+, phosphate supplements and cystagon was started at the age of 10 months. He was admitted to the hospital at the age of one year with vomiting, severe dehydration, metabolic disturbances and unfortunately expired after five days. Table 1 shows a summary of the clinical picture, age of presentation, organs involved and complications, in each case.

DISCUSSION

Cystinosis is a rare autosomal recessive lysosomal storage disorder, with an estimated incidence of one in 200,000 live births. It is characterized by an accumulation of the amino acid cystine in lysosomes throughout the body with crystal formation in various tissues and organs. The responsible gene CTNS, encoding the lysosomal cystine carrier cystinosin, has been cloned in 1998 and is located on the short arm of the chromosome 17[3]. Depending on the age at presentation and the degree of disease severity, the three clinical forms of cystinosis are:

1. Nephropathic infantile form which is the most frequent and most severe form of the disease
2. Nephropathic juvenile form: intermediate cystinosis, late-onset form, adolescent form
3. Non-nephropathic adult form: benign non-nephropathic cystinosis, ocular non-nephropathic cystinosis

All three forms of the disease are caused by mutations of the CTNS gene and have phenotypic overlap.

Patients with INC are generally born from uneventful pregnancies and have normal birth weight and length. Despite cystine accumulation starting *in utero* clinical symptoms are absent at birth and gradually develop during the first few months of life. The kidneys are the first affected organs, and progressively lose function of their proximal tubular transporters, resulting in urinary loss of water, Na^+, K^+, bicarbonate, Ca^{2++}, Mg^{2++}, phosphate, amino acids, glucose, proteins, and many other solutes reabsorbed in this nephron segment. This generalized proximal tubular dysfunction is called "renal Fanconi syndrome"[4].

The diagnosis of INC can be missed during the first months of life, especially when only a limited number of urinary markers are used to identify renal Fanconi syndrome.

At the age of 6 - 12 months, full-blown Fanconi syndrome is usually present and causes clinical symptoms of polyuria, thirst, failure to thrive, growth retardation, vomiting, periods of dehydration, constipation, and rickets, as was seen in all our cases. Growth failure is due to metabolic acidosis, rickets, feeding problems, cystine storage in growth plates, and impairment of endocrine organs .

Biochemically, the patients present with hypokalemia, hypophosphatemia, metabolic acidosis, low serum uric acid, low carnitine, and sometimes, hyponatremia[5]. Occasionally, hypokalemia in combination with hypochloremic metabolic alkalosis and elevated plasma renin activity can mimic Barter syndrome, (as in case No. 4). The concomitant presence of symptoms of proximal tubular dysfunction such as aminoaciduria, glucosuria, and phosphaturia should not allow the diagnosis of cystinosis to be missed[6].

Proteinuria can reach many grams per day, and consists of LMW proteins, albumin, and high molecular weight proteins. Excessive losses of calcium and phosphate can cause the development of nephrocalcinosis and the formation of renal stones.

In most patients, the glomerular filtration rate (GFR) remains normal for up to two years and then progressively deteriorates towards end stage renal disease (ESRD) at the end of the first decade. Both hemodialysis and peritoneal dialysis are suitable for renal replacement therapy (RRT) in cystinosis patients. Renal transplantation is the treatment of choice in patients with ESRD, as the disease does not recur in the grafted organ[7].

Renal biopsy is not required for the diagnosis of cystinosis, and therefore, the descriptions of renal histology at early stages of the disease are limited[8,9].

Corneal cystine crystals are absent at birth and generally can be observed by an experienced ophthalmologist with slit lamp examination at the age of one year. These crystals cause reflections of light and result in photophobia with substantial discomfort. Untreated teenagers may develop painful corneal erosions, punctate, filamentous or band keratopathy, iris crystals, and peripheral corneal neovascularization[10,11].

The continuing multi-organ accumulation of cystine crystals leads to impairment of endocrine organs. Hypothyroidism is found in up to 70% of untreated cystinosis patient older than 10 years. Impaired insulin production can be exacerbated by steroid therapy after renal transplantation and results in insulin-dependent diabetes mellitus. Male and female patients achieve pubertal events in normal sequence but puberty is delayed[12].

Myopathy manifests with swallowing difficulties, decreased tongue and lip strength, small-muscle wasting and hypophonic speech. CNS involvement is manifested as seizures, tremors, mental retardation or pyramidal syndrome. IQ values are in normal range. Peripheral nervous system is normal. Psychosocial problems due to chronic illness may be seen.

Other reported extra-renal symptoms include decreased skin and hair pigmentation (in patients of European descent), impaired sweating which predisposes them to hyperthermia, exocrine pancreas deficiency, portal hypertension, hypersplenism and cystinotic bone disease[13]. The latter is multifactorial in nature and is attributed to losses of calcium, phosphate, and vitamin D, cystine accumulation in the bone, and uremic osteodystrophy. Patients of African or Middle Eastern origin can have dark hair and dark skin, which should not exclude the diagnosis.

Cystinosis should be suspected in all patients with failure to thrive and sign of renal Fanconi syndrome

as it is the most common cause of inherited Fanconi syndrome in children. The detection of elevated intracellular cystine content is the cornerstone for diagnosis. The methods for cystine determination differ depending on the cell type: mixed leukocyte preparation or polymorphonuclear (PMN) leukocytes. Tandem mass spectrometry (tandem MS) is the most sensitive method and is currently widely used for cystine determination in cystinosis[14]. Each laboratory performing cystine measurements should provide their own reference values in patients at the time of diagnosis, and also for heterozygote and healthy subjects. Reference values, provided by our laboratory PMN cystine levels are as follows: in healthy subjects: 0.04 - 0.1; in heterozygotes: 0.14 - 0.57; in patients at diagnosis: > 1.

Molecular analysis of the cystinosin gene allows early diagnosis and can be used for prenatal diagnosis of the disease. Prenatal diagnosis of cystinosis can also be made by measuring 35S-labeled cystine accumulation in cultured amniocytes or chorionic villi samples (CVS); and by a direct measurement of cystine in uncultured CVS[15].

Since the cloning of CTNS in 1998, over 90 mutations have been reported, with a detection ratio close to 100%[16]. A genotype-phenotype correlation related to the clinical forms of cystinosis is observed, with severe truncating mutations mostly found in patients with the infantile form of the disease and at least one mutation allowing the residual function of cystinosin in patients with intermediate or adult cystinosis[17].

After one year of age, the observation of cystine crystals in the cornea is pathognomonic for cystinosis, whereas the absence of the crystals excludes the diagnosis after the age of two years. Patients with the juvenile form of cystinosis also invariably demonstrate corneal cystine crystals.

All patients with cystinosis should have free access to water and toilet, because of pronounced polyuria and polydipsia. Prolonged exposure to heat and sun should be avoided because of photophobia, the risk of dehydration and / or heat stroke due to impaired sweating.

The aim of symptomatic therapy in patients presenting with Fanconi syndrome is the maintenance of fluid and electrolyte balance, good nutrition and prevention of rickets. The dose of potassium, sodium, bicarbonate, and phosphate varies substantially and shall be regularly adapted according to serum values. 1, 25 - dihydroxycholecalciferol supplementation should be used starting from early childhood. However, excessive administration of phosphate, 1, 25 - dihydroxycholecalciferol and bicarbonate may aggravate the development of nephrocalcinosis or stimulate renal stone formation. Calcium supplementation is generally not indicated. Poor appetite, vomiting, and oral motor dysfunction often require a nasogastric tube or gastrostomy feeding, especially in young children.

Treatment with recombinant growth hormone results in catch-up growth and further maintenance of growth velocity. Growth hormone is frequently not required in patients treated with cysteamine, especially when started at an early age, as cysteamine by itself improves growth[18]. Other complications, such as hypothyroidism, diabetes, or hypogonadism, are considered for treatment with levothyroxin, insulin, and testosterone respectively.

Specific treatment is with cysteamine. The amino-thiol cysteamine depletes lysosomal cystine content by a disulfide exchange reaction with cystine, resulting in the formation of cysteine-cysteamine mixed disulfide and cysteine. Cysteine-cysteamine mixed disulfide exits lysosomes *via* a "system c" transporter and the remaining cysteine *via* a cysteine carrier. The administration of cysteamine at 1.3 - 1.9 g/m^2 in four daily doses drastically lowers the cystine content of the lysosomes, postpones or even prevents the deterioration of renal function and the development of extra-renal complications. Furthermore, cysteamine treatment improves growth[19]. Cysteamine should be administered as soon as the diagnosis of cystinosis is made, and continued lifelong, even after renal transplantation to protect the extrarenal organs. The side effects of cysteamine are mostly restricted to gastrointestinal discomfort (due to the release of gastrin and the resulting stimulation of H^+ secretion in the stomach). Gastric acid hypersecretion and ulcerogenicity of cysteamine can be improved by the administration of proton pump inhibitors.

For monitoring cysteamine therapy blood should be drawn 6 h after the last intake of the drug. Regular measurements of cystine in PMN leukocytes are required in order to adjust cysteamine dose. Unfortunately, in the majority of patients cysteamine cannot reverse Fanconi syndrome and only postpones the development of renal failure[20].

Since systemic cysteamine treatment has no effect on corneal cystine crystals, topical 0.5 % cysteamine eye drops are indicated. These drops are highly effective and when administered 6 - 12 times daily are able to dissolve corneal cystine crystals completely within 8 to 41 months, even at a later age.

Infants and children with cystinosis who have renal Fanconi syndrome should be examined frequently (at least four times a year) to monitor growth and the nutritional state, metabolic control of Fanconi syndrome, and white blood cell cystine measurements for adjusting cysteamine dose. Ophthalmic control, including slit-lamp examination and fundoscopy, at a

minimum of once a year, is mandatory. Starting from the end of the first decade of life, special attention should be paid to the possible appearance of extra-renal complications.

CONCLUSION

In all patients presenting with failure to thrive during the first years of life, renal Fanconi syndrome should be excluded. The true diagnosis of cystinosis is based on the measurement of elevated cystine content in blood cells, and molecular analysis of the CTNS gene. Cysteamine is currently the only available treatment interfering with the disease pathogenesis. However, new treatment modalities may become available in the future.

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Case Report

Solitary Mucormycosis in Renal Allograft: A Case Report

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ABSTRACT

Mucormycosis is a known infection in renal transplantation responsible for mortality and morbidity in this group of patients. However, solitary mucormycosis in renal allograft is uncommon. We present a patient with solitary mucormycosis in the renal allograft suspected as pyonephrosis. Graft nephrectomy at one and half months after diagnosis and two and half months post-transplant was performed. The patient is clinically stable and on maintenance dialysis, without evidence of any infection subsequently.

KEY WORD: nephrectomy, pyonephrosis, renal transplantation

INTRODUCTION

Infection continues to be a significant cause of morbidity and mortality in renal transplant (RTx) recipients due to their susceptibility to opportunistic infections[1,2]. Mycotic diseases in these patients are usually fatal due to difficulty in diagnosis and management. Mucormycosis is caused by the order mucorales of fungi, generally affecting patients with definite predisposing factors, is rapidly progressive and frequently fatal in RTx patients. Various manifestations have been described, predominant forms being rhinocerebral, pulmonary, gastrointestinal, cutaneous and disseminated. Rarely, mucormycosis develops in the renal allograft itself[3,4].

We present a case of solitary mucormycosis in the renal allograft which required graft nephrectomy to salvage the patient.

CASE HISTORY

A 42-year-old man with hypertension associated end stage renal disease and hypothyroidism since four years presented to our outpatient clinic for RTx. He was initiated on hemodialysis (HD) and underwent RTx eight months later with an unrelated donor (mother-in-law, HLA match: 1/6) under cover of 500 mg iv methylprednisone (MP) for three days. Maintenance immunosuppression was prednisone, 20 mg/day, tacrolimus, 0.08 mg/kg/day and mycofenolate mofetil (MMF), 360 mg twice a day (BID). Postoperative course was smooth and nadir serum creatinine (SCr) was 1.36 mg/dl. He was discharged on 15th postoperative day. Four weeks post-transplantation he was admitted with complaints of burning micturition and hematuria for two days accompanied by graft tenderness and low grade fever with maintained urine output. Investigations revealed: hemoglobin, 11.8 gm/dl, total leucocyte count, 12.4 x 10^3/ul, urine albumin-absent, microscopy – 15 - 17 pus cells and 6 - 8 RBCs /high power field (HPF), S Cr, 2.66 mg/dl and blood urea, 67 mg/dl. Ultrasonography (US) of the renal allograft revealed a kidney size of 10.8 x 6.1 cm, normal echopattern with maintained cortico-medullary differentiation. However, mild hydronephrosis and hydroureter in upper segment was noted. Doppler showed enhanced echopattern and resistivity index (RI) of 0.81 favoring pyonephrosis. No

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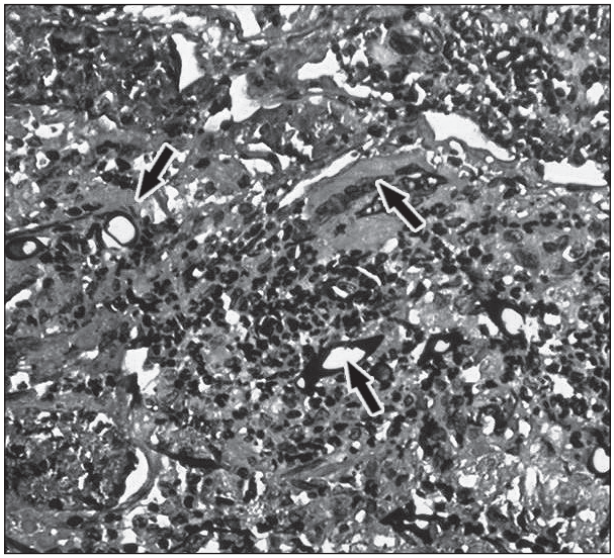

Fig. 1: Renal allograft biopsy: Jone's silver methaneamine stain, x 100, showing giant cell (arrow head) with fungal buds (arrows)

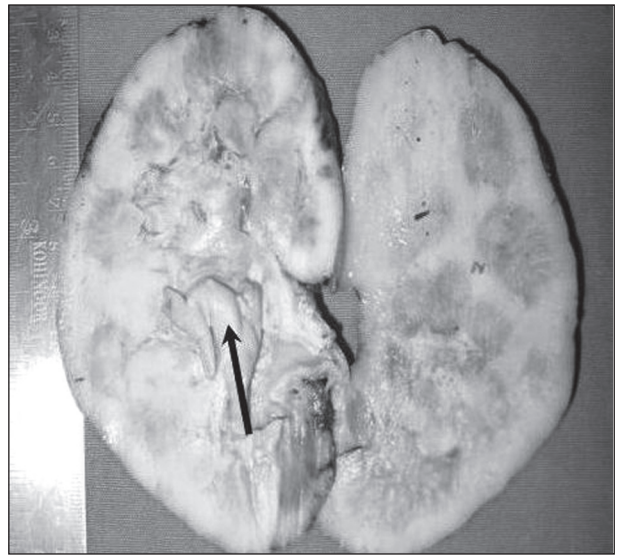

Fig. 2 A: Renal allograft, cut section showing pelvi-calyceal system filled with necrotic tissue

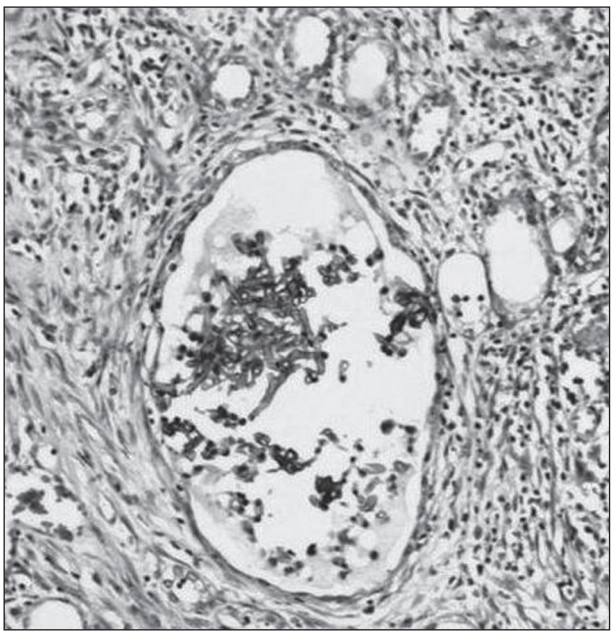

Fig. 2 B: Renal allograft: H & E stain, x 100, showing tubular lumen filled with fungal buds and hyphae

perigraft collection was noted. He was treated with 4-aminoglycosides, 250 mg, four times per day for seven days. Percutaneous nephrostomy tube (PCN) was inserted and left in-situ for two days. No output was noted from the PCN tube. Serum creatinine increased to 5.17 mg/dl, urine albumin was 1+ and microscopy showed 45 - 50 pus cells / HPF. The urine / blood cultures were sterile and no acid fast bacilli were observed in urine. Ten days later he was subjected to ureteric re-implantation with DJ stent and graft biopsy was performed subsequently. Histopathology revealed pyonephrosis with microabscesses and presence of fungal buds and non-septate hyphae with wide-angled branching and associated Langhan's and foreign body giant cell reaction diagnosed as mucormycosis (Fig. 1). No evidence of any kind of infection was noted anywhere else. He was treated with Targocid 300 mg BD and Ambisome100 mg IV x 14 days. DJ stent was removed after a week, culture of fluid / DJ tip and urine was sterile. No fungal growth was observed. His S Cr increased to 5.98 mg/dl, urine showed faint traces of albumin, microscopy had persistent sterile pyuria with 150 - 160 pus cells and 8-10 RBCs / HPF. Doppler graft showed a kidney size of 11 x 5.8 cm with mild hydronephrosis (HN) and hydroureter (HU) and echogenic material in the pelvi-calyceal system, suggestive of pyonephrosis. Forty milli litre collection at upper pole and five milli litre collection in graft bed was now seen with RI of 0.79. All immunosuppression was stopped since the biopsy. However, urine output remained 4 - 5 liters a day throughout this period. Clinically the patient was stable and afebrile. His urine examination, however, showed persistent pyuria and creatinine clearance was not established. Eventually to save his life, he was subjected to graft nephrectomy three and half months post-transplant. Graft was enlarged, swollen on external examination and on cutting pus exuded out from pelvi-calyceal system which was packed with necrotic material along with fungal ball (Fig. 2a). Microscopic examination revealed tubular lumina filled with fungal hyphae. Giant cell reaction noted in the parenchyma, glomeruli and vessels was unremarkable for immune injury or fungal or viral infections; necrotic tissue showed only fungal buds and hyphae amidst scanty necrotic tissue (Fig. 2b). At one week post-nephrectomy, his urine was sterile and unremarkable for pyuria on microscopy. The patient is now on maintenance HD with antifungal coverage

for two months and has no evidence of fungal / other infections anywhere in the body.

DISCUSSION

Despite ongoing improvements in immuno-suppressive therapy and surgical techniques, fungal infections remain a significant cause of morbidity / mortality in organ transplant recipients[2]. The overall incidence of invasive fungal infections in RTx recipients ranges between 0 - 14%. However, these have a rapid downhill course. Mucormycosis accounts for 1 - 9% of all invasive mycoses and is associated with mortality rate as high as 64%[3]. Multiple risk factors which include diabetes, chronic liver disease, operative technical errors, re-operation / transplantation, duration of transplant procedure, post-operative HD and use of monoclonal antibodies place the organ transplant recipient at increased risk for fungal infections. The mode of entry is through respiratory or digestive tract, or damaged skin barriers. Rhinocerebral mucormycosis is the most common mucormycosis presentation in RTx recipients[1,2,5]. In the present case, introduction of infection through PCN procedure or re-exploration for re-implantation of ureter (1 month post-transplant) seem to be the probable portal of entry for the fungal spores.

More than 90% of fungal infections belong to fungi imperfectii, like aspergillosis, candidiasis, mucormycosis, coccidiodomycosis, histoplasmosis and paracoccidiodo-mycosis. Zygomycosis is a ubiquitous fungus and is found in decaying vegetative organic matter. They have minimal intrinsic pathogenicity, but can cause grave and often fatal infection in immune-compromised hosts. Overall survival for different forms of mucormycosis varies from 33 - 100%. Mortality in isolated renal mucormycosis is 52%. The standard practice in management of mucormycosis in renal transplant patients is discontinuation of immunosuppression and intravenous administration of liposomal amphotericin B, 3 - 5 mg/kg BW for 2 - 3 weeks. The aim in such therapy is to save the patient at the cost of allograft. We managed our patient on the same line. However, due to persistent pyuria and graft dysfunction, graft nephrectomy had to be undertaken to save life[6-8]. Most probably, our patient did not succumb to this infection due to maintained urine output and withdrawal of immunosuppression.

CONCLUSION

Mucormycosis is a rare complication of RTx and may not be eradicated even with prolonged liposomal anti-fungal treatment. Timely graft nephrectomy can save the life of such patients.

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Case Report

Leiomyoma of the Epididymis: A Case Report and Review of the Literature

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ABSTRACT

Tumors of the epididymis, whether benign or malignant, primary or secondary are very rare. Adenomatoid tumors and leiomyomas are the most frequently diagnosed benign tumors of the epididymis. We report a case of a left-sided asymptomatic leiomyoma of the epididymis in a 39-year-old Asian man who presented with an inguinal hernia on the right side. Ultrasonography was suggestive of adenomatoid tumor of the epididymis. Surgical exploration was done through an inguinal incision with conservative excision of the benign looking mass of the tail of the epididymis. Frozen section was not performed because of clinical suspicion of tuberculosis. Histopathological examination revealed an epididymal leiomyoma. Herein, we report this case and review the relevant literature.

KEY WORDS: epididymal leiomyoma, extratesticular tumors, scrotal mass, sonography

INTRODUCTION

Paratesticular tumors are rare but generally benign and are usually treated by local excision[1]. Epididymal leiomyomas are well defined, surrounded by a gray-whitish fibrous capsule and are usually 1 - 4 cm in size. These tumors tend to be asymptomatic and painless and appear to occur with equal frequency on the right and left side. A long history of upto 40 years prior to surgical excision has been described[2]. In this case, the epididymal mass was discovered accidentally. Bilateral lesions are extremely rare but do occur[3].

CASE REPORT

A 39-year-old Asian man presented to our surgical outpatient clinic with a right inguinal hernia. He was married and had four children. On physical examination there was a reducible right inguinal hernia. Scrotal examination showed a smooth round and firm mass infero-posterior to normally felt left testicle. The mass measured 3 x 4 cm with no transillumination and neither tenderness nor erythema was noted. There was no history of testicular trauma. Laboratory studies showed normal blood cell count, renal and liver functions. Tumor markers including α- fetoprotein and β-human chorionic gonadotropin were within normal range. Ultrasonography (US) revealed a heterogeneous well- defined mass 4 cm in diameter showing a whorling appearance (Fig. 1) and arising from the tail of the epididymis and lying below the left testis (Fig. 2). Both testicles looked normal. Adenomatoid tumor of the left epididymis was suggested. Since the patient was an Asian, where tuberculosis is considered in the differential diagnosis of any epididymal lesion, frozen section was not planned and consent for left orchidectomy was obtained. Through a left inguinal incision, the left testis was explored by Chevassu maneuver (vascular clamping of the cord). There was minimal hydrocele along with a well-circumscribed, round and firm 4 cm mass with whitish grayish capsule. This mass could be easily excised from the tail of the epididymis.

The patient had an uneventful postoperative recovery. Histological examination of the mass showed grossly circumscribed nodular lesion with fibrotic whorly cut section measuring 4 cm in maximum diameter. Microscopic section revealed a spindle cell tumor composed of fascicles of smooth muscle cells with elongated blunt ended nuclei, no atypia and rare mitosis (Fig. 3). ASMA staining was positive with a final diagnosis of epididymal lesion compatible with leiomyoma. No evidence of local recurrence was found during a two-year of follow-up.

DISCUSSION

Leiomyoma of the genitourinary tract may originate from any structure containing smooth

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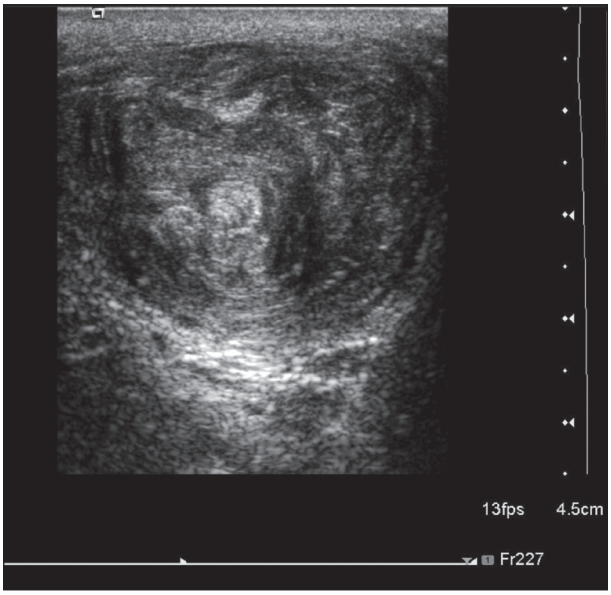

Fig. 1: Sonogram TS showing the whorly appearance of the tumor

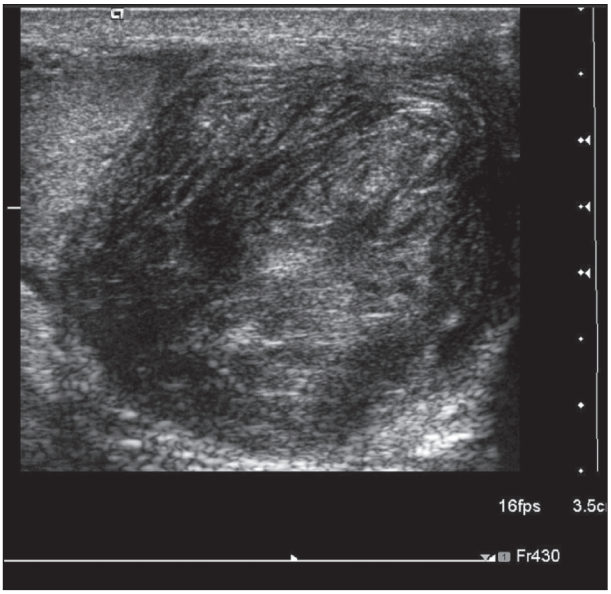

Fig. 2: Sonogram LS shows the leiomyoma distal to the testis

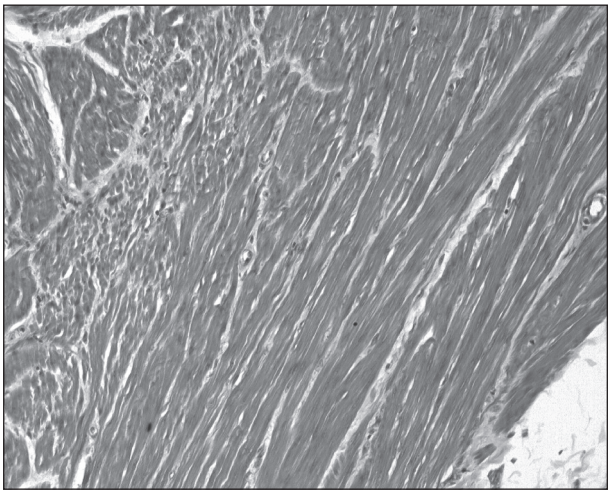

Fig. 3: Fascicles of smooth muscle cells with elongated blunt ended nuclei (Hematoxylin and Eosin 200X)

muscle. After the uterus the most common site is the renal capsule and they have been described in the ureter, bladder, urethra, prostate, seminal vesicles, spermatic cord, testis, epididymis, penis and scrotum[4].

Epididymal leiomyoma is the second most common primary tumor of the epididymis comprising 6% of epididymal tumors. Although patient age varies widely the tumor most commonly manifests in the fifth decade of life as a slow growing non-tender scrotal mass[5]. The incidence of epididymal leiomyoma in white people is estimated to be 5% of epididymal masses as opposed to 40% of epididymal masses in Asian people[6]. US is a widely used imaging modality for patients suspected to have scrotal abnormalities. Leiomyomas have a variable ultrasonographic appearance, depending on whether it is predominantly solid or cystic and may contain calcifications; they frequently involve the glomus major and may be associated with hydrocele in 50% of cases[7]. Frates *et al* found that US is not successful in uniquely correlating extratesticular masses with their malignant potential[8].

Usually US is the initial radiologic imaging modality of choice in 90% of cases and is enough to localize the lesion. However, in 10% of patients in whom location and origin of mass is still unknown after US, MRI can be used[9]. As radiography imaging alone is insufficient to determine whether paratesticular masses are malignant, scrotal exploration is often advised. An inguinal approach should be used to allow control of the lymphatic drainage of the testis. The testicular artery and other cord structures should be controlled and clamped to prevent lymphatic and hematogeneous spread of the disease. Cooling of the exposed testis and epididymis at the time of vascular control has been described to minimize ischemic time. Intraoperative frozen section can be used for on spot decisions regarding the possibility of testicular preservation[10].

In general, intraoperative frozen section analysis of testicular tumors correlate extremely well with final pathology[11]. Although we had consent for orchieodectomy decision to perform a testis sparing procedure was taken based on clinical, sonographic and macroscopic appearance of the mass. Although it is presumed that epididymal leiomyomas are benign in nature and do not recur, regular outpatient follow-up and sonographic examination are still recommended[12]..

CONCLUSION

Epididymal leiomyomas are rare benign tumors. Sonography is safe and reliable method to confirm and characterize an epididymal mass. However, surgical exploration is advised with organ sparing excision and when in doubt intraoperative frozen section can be used. A careful postoperative outpatient follow-up is recommended.

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Case Report

Walker-Warburg Syndrome Features and Gene Study: A Report of Two Cases

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ABSTRACT

Walker-Warburg syndrome (WWS) is a rare autosomal recessive disorder characterized by congenital muscular dystrophy (CMD) and brain and eye abnormalities. Two other diseases have similar features, namely, muscle-eye-brain disease (MED) and Fukuyama congenital muscular dystrophy (FCMD). The brain abnormalities in WWS are characterized by type 2 cobblestone lissencephaly, hydrocephalus, cerebellar malformations and brain stem anomalies. Mutations in protein O-mannosyltransferase 1 and 2 (POMT1 and POMT2) genes were found in 20% of WWS cases. Other rare mutations were found in Fukutin and Fukutin-related protein (FKRP) genes. We report cases of two Kuwaiti boys with WWS, who had typical brain magnetic resonance imaging (MRI) features. Both were screened for POMT1, POMT2, POMGnT1, FKRP and LARGE gene mutations and were negative. To the best of our knowledge these are the first two cases to be screened for known WWS gene mutations in Kuwait.

KEY WORDS: autosomal recessive disorder, gene mutation, MRI

INTRODUCTION

Dystrophin glycoprotein complex (DGC) is an assembly of proteins spanning the sacrolema of skeletal muscle cells[1]. Dystroglycan (dystrophin-associated glycoprotein) is a major component of (DGC), which is expressed in many cell types and is synthesized as a precursor propeptide that is post-translationally cleaved and differentially glycosylated to alpha dystroglycans (alpha DG)[2]. The highly glycosylated alpha DG is one of the major dystrophin–associated proteins anchored at basement membrane protein, laminin 2, to dystrophin molecule. The disorders associated with defective glycosylation are now categorized as dystroglycanopathies which include Fukuyama congenital muscular dystrophy (FCMD), muscle-eye-brain (MEB) disease, Walker-Warburg syndrome (WWS), diseases with mutations in fukutin-related protein (FKRP) and LARGE genes. WWS is proved to have mutations in the glycosyltransferase genes (POMT1)[3]. It is the most extreme form of CMD, which shows the most severe brain malformation, associated with neuronal migration abnormalities (often type II lissencephaly) and eye involvement[4]. Type II lissencephaly also known as cobblestone complex is caused by neuronal overmigration, during neocortex lamination, that gives rise to disorganized cerebral cortex and multiple coarse gyri with agyric regions.

CASE HISTORY

Case I

A Kuwaiti boy was born to a first degree cousin at a gestational age of 35 weeks by emergency cesarian section after a failed vacuum extraction. His birth weight was 2.2 kg (2nd centile), height was 46 cm (3rd centile) and head circumference was 36 cm (98th centile). He had two normal siblings. Antenatal ultrasound showed hydrocephalus. Examination at birth revealed a weak child with low set ears, generalized hypotonia, hyporeflexia, very weak suckling reflex and bilateral hydrocele. No encephalocele was detected.

Complete blood count (CBC), liver function tests (LFT), renal function tests (RFT), serum electrolytes (SE) and blood sugar (RBS) were all within normal range. TORCH screening for the baby and his mother was negative as also the basic screening for inborn errors of metabolism. Computerized tomography (CT) scan for the brain (Fig. 1) at the age of six days showed marked communicating hydrocephalus. A ventriculo-peritoneal shunt was inserted. He developed generalized convulsions at the age of five months and MRI revealed cobblestone lissencephaly,

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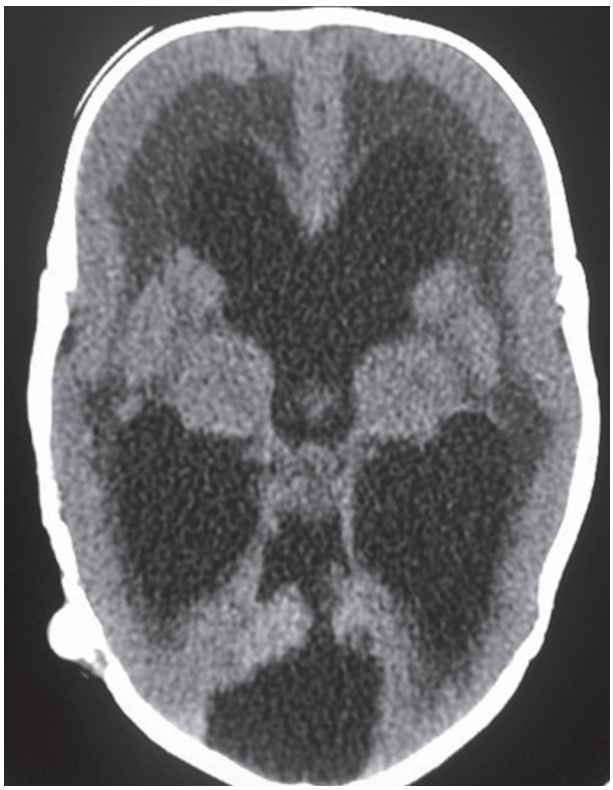

Fig. 1: CT, plain axial cuts without iv contrast, showing hydrocephalus (ventriculomegaly) involving third, fourth and lateral ventricles, Thick gyri and shallow sulci are noted.

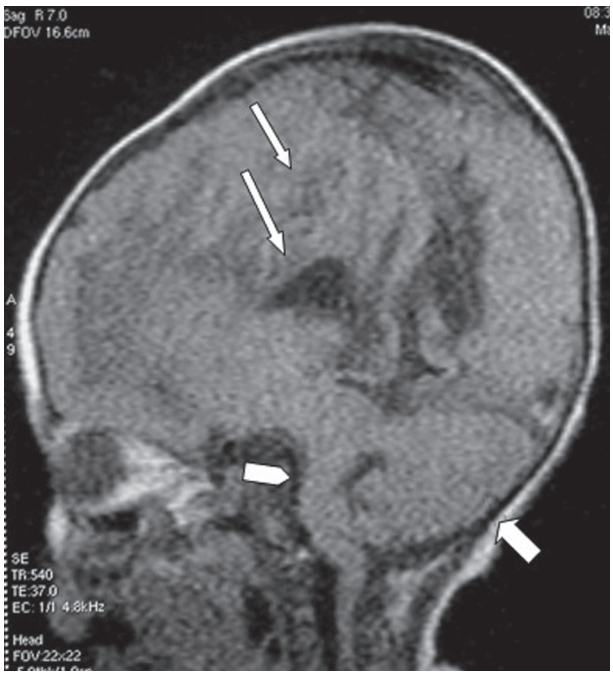

Fig. 3: MRI, T1 WI, Saggital, showing small sized cerebellum (cerebellar hypoplasia) (short arrow), kinking of the pons (arrow head) and corpus callosum hypoplasia (long arrow).

hypomyelination of the white matter in both cerebral hemispheres (Fig. 2), mildly hypoplastic pons with abnormal dorsal kink, hypogenesis of corpus callosum,

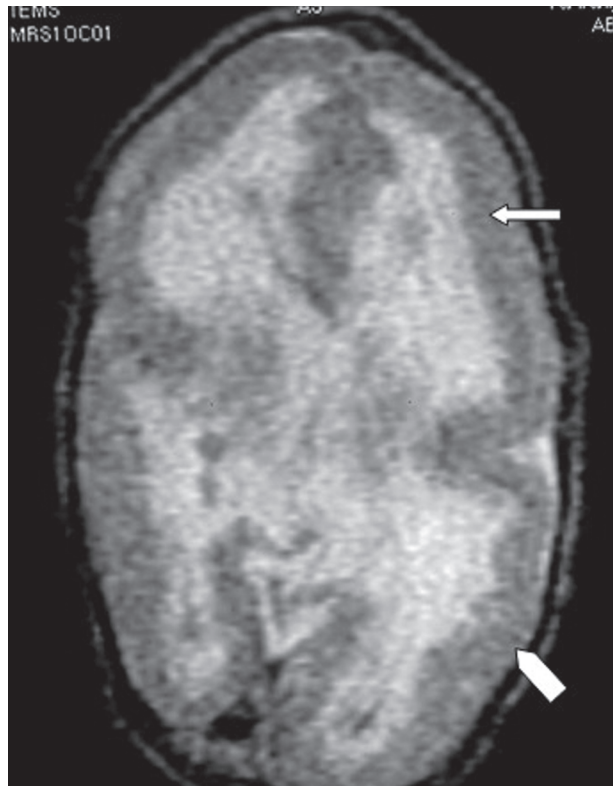

Fig. 2: WWS, type II lissencephaly (cobblestone appearance), MRI, axial cuts T2 WI. There is cortical thickening with abnormal gyri and shallow sulci (arrow). The cortex shows a bumpy surface (arrow head). Underlying white matter is abnormally hyperintense due to abnormal myelination.

absent septum pellucidum and smaller right ocular globe compared to the left (Fig. 3). These findings suggested a diagnosis of WWS. Other investigations including serum creatinine phosphokinase (CK, 3000 IU/l), and electromyography (EMG) was consistent with pronounced myopathic abnormalities. Electroencephalogram (EEG) showed abnormal record with slow background and generalized rhythmic slow waves. Eye examination revealed bilateral cataract, lost anterior chamber, retinal dysplasia, atrophic optic disc and right microphthalmia.

Screening for mutations in POMT1, POMT2, protein O-linked mannose B1, 2-N-acetylglucosami nyltransferase1 (POMGnT1), FKRP and LARGE (Lac etylglucosaminyltransferase-like protein) genes was negative. This patient had progressive developmental delay, recurrent aspiration with recurrent respiratory tract infection and died at the age of 30 months.

Case II

This Kuwaiti boy was born to first degree cousin at term by cesarian section. His birth weight was 3.2 kg (25th centile), height was 47cm (50th centile) and head circumference was 43.5 cm (> 98th centile). He had two healthy brothers and one sister with WWS who died at the age of one year. Examination at birth

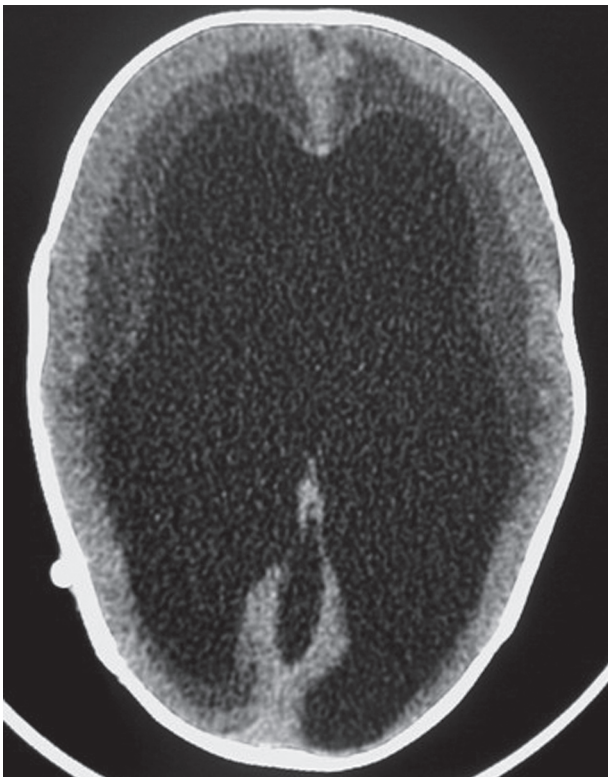

Fig. 4: CT, plain axial cuts, marked ventriculomegaly with thick cortex and shallow sulci (lissencephaly).

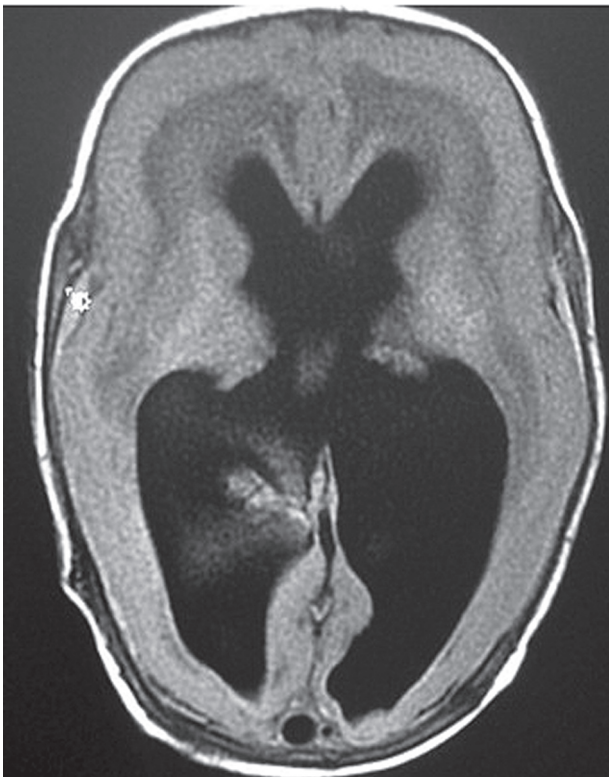

Fig. 5: MRI, axial T1 WI, lissencephaly, displays figure of eight shape of the brain, flat surface of the brain due to lack of sulcation and the Sylvian fissures are shallow and vertically oriented. Thickened cortex is also noted.

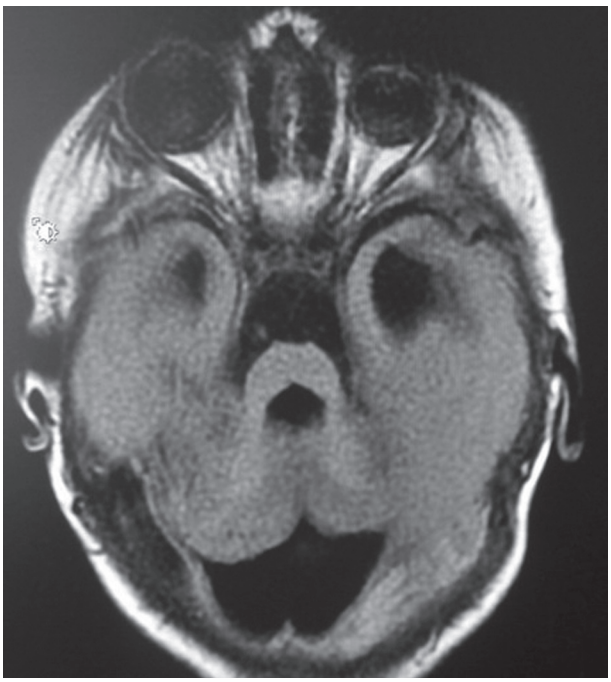

Fig. 6: MRI, axial T1 WI, unequal size of the eye globe (small left eye), ventriculomegaly with cerebellar hypoplasia.

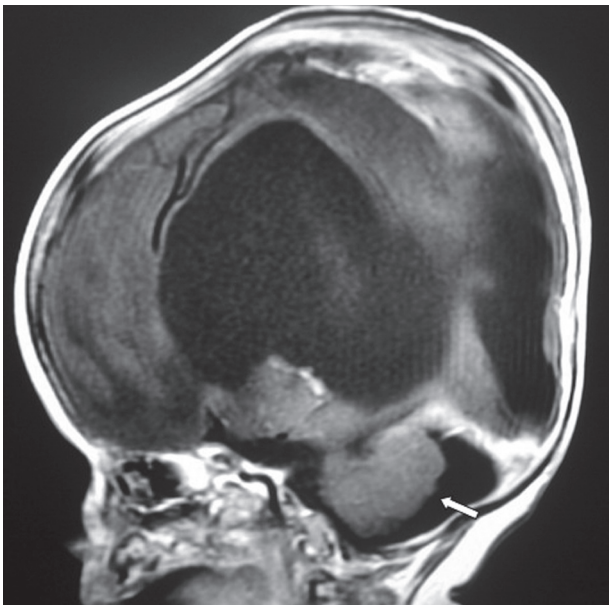

Fig. 7: MRI, Sagittal T1 WI. Dilated supra and infra-tentorial ventricular system, including lateral, third and fourth ventricles, with shallow sulci thick cortex (lissencephaly) and cerebellar hypoplasia (arrow)

revealed significant large head with low set ears. He was hypotonic with weak cry and weak suckling reflex, weak muscle power and absent deep tendon reflexes. He had also bilateral undescended testes. No encephalocele was detected.

Eye examination showed bilateral corneal opacity, cataract, shallow anterior chamber, hyperplastic vitreous, optic nerve atrophy, asymmetrical retinal detachment and left microphthalmia.

CBC, LFT, RFT, SE, RBS, TORCH and basic metabolic screening were all normal. CK was (2790 IU/l). EEG showed abnormal record. EMG showed significant myopathic changes. CT head revealed obstructive hydrocephalus and hypoplastic vermis (Fig. 4). MRI head showed thickened cortex with lissencephaly, hydrocephalus, shallow sylvian fissures, hypomyelination (Fig. 5), hypogenesis of corpus callosum, pons and vermis, cerebellar hypoplasia and left microphthalmia (Fig. 6) and (Fig. 7).

Gene study and screening for mutations in POMT1, POMT2, POMGnT1, FKRP and LARGE genes were negative.

He was managed with ventriculo-peritoneal shunt, antiepileptic drugs and physiotherapy. He had global developmental delay with recurrent chest infection and he died at the age of two years.

DISCUSSION

Both our cases showed most of the clinical criteria of WWS. Both of them had CMD based on severe muscle weakness, hypotonia, hyporeflexia, high CK, myopathic changes in EMG and characteristic MRI brain and eye abnormalities. Furthermore both of them had low set ears. Moreover, case I had bilateral hydrocele, and case II had undescended testes. Both cases ran a severe course with recurrent respiratory tract infection and both died before the age of three years[5,6].

We screened our patients for mutations in POMT1, POMT2, POMGnT1, FKRP and LARGE genes but unfortunately no mutation could be detected.

WWS is the most severe form of CMD with most children dying before the age of three years. Warburg (1976, 1978) proposed autosomal recessive inheritance when she observed the association of hydrocephalus and congenital retinal detachment in the son of first cousin parents among 15 cases that she reported[7,8].

CMD disorders are now categorized as dystroglycanopathies which include FCMD, MEB, WWS and diseases with mutations in Fukutin-related protein (FKRP) and LARGE genes. Among them, MEB and WWS were proven to have mutations in the glycosyltransferase genes. Beltran-Valero de Bernabe *et al* screened WWS patients for mutations in the gene encoding POMT that plays a vital role in synthesizing the substrate for POMGnT1. Homozygous mutations at the POMT1 locus on chromosome 9q34 were found in five out of 15 consanguineous families with WWS[9]. In another series of 30 patients with classic WWS, two potential novel heterozygous mutations in the POMT1 gene were found in two patients from non-consanguineous parents. However, the other 28 patients failed to show any POMT1 mutations. Linkage analysis in six consanguineous families with WWS showed that defective POMT1 was an uncommon cause of WWS in this population (less than 7%)[10]. One child with the WWS phenotype was reported to have a homozygous null mutation in the Fuktin gene and another child was homozygous for C953T missense mutation in the FKRP gene[11-13]. A fourth causative gene for WWS was found in 2005, when three homozygous mutations in the POMT2 gene were detected in WWS patients from three families[14]. Although gene mutations are currently unknown in majority of patients, only 10 - 20% of cases have a mutation in the POMT1, POMT2, Fukutin or FKRP genes[5]. WWS can be diagnosed on the basis of the four criteria described by Dobyns in 1989[15]. These criteria are: (1) CMD characterized by hypoglycosylation of alpha dystroglycan, (2) High CK level, (3) anterior eye anomalies (cataract, shallow anterior chamber, microcornea and microphthalmia, and lens defects) and posterior eye anomalies (retinal detachment or dysplasia, hypoplasia or atrophy of the optic nerve and macula and cloboma), (4) migrational brain defect with type 2 lissencephaly, hydrocephalus, vermal or general cerebellar hypoplasia and flat brain stem and white matter hypomyelination. Additional brain anomalies such as hypoplasia / agenesis of corpus callosum, occipital encephalocele and Dandy-Walker malformation have been described[16]. Other associated anomalies which have been described are small penis, undescended testes and rarely other facial dysmorphic features such as low set ears and cleft lip or palate[5]. MEB disease and FCMD are two other rare autosomal recessive disorders sharing the combination of CMD and brain malformations with WWS. Lack of consistent ocular abnormalities in FCMD allowed a clear clinical demarcation between this syndrome and WWS. The phenotypic distinction between MEB and WWS has remained controversial although the brain abnormalities are more severe in WWS[17,18].

CONCLUSION

WWS is a rare lethal autosomal recessive disease. It should be considered in the differential diagnosis of hypotonia in infants. Gene mutations are defined in 10 - 20% of cases only. Although diagnosis can be done on clinical and radiological criteria, gene screening should be considered for proper risk calculation.

ACKNOWLEDGMENT

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Case Report

F-18 FDG PET/CT Imaging of Tuberculous Lymphadenopathy Mimicking Lymphoma: A Case Report

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ABSTRACT

We report a case of pulmonary tuberculous lymphadenopathy in an asymptomatic 19-year-old female. Thoracic computed tomography (CT) scan showed enlargement of lymph nodes in right neck, mediastinum and left hilum with heterogeneous contrast enhancement. Positron emission tomography (PET) / CT with F-18-fluorodeoxyglucose (F-18-FDG) demonstrated significantly increased metabolic activity of the lymph nodes. The lesions were diagnosed as tuberculous lymphadenopathy by histopathologic examination.

KEY WORDS: infectious disease, lesions, tuberculosis, lymphoma

INTRODUCTION

Tuberculosis is one of the most common infectious diseases and it has shown increasing morbidity in recent years[1]. However, diagnosis of tuberculous lymphadenopathy in adults with non-invasive examination is difficult. It may be misdiagnosed as lymphoma, sarcoidosis or as metastatic lymph nodes due to the absence of typical clinical symptoms, active pulmonary tuberculosis, or positive laboratory results. Currently, F-18 FDG PET/CT imaging is increasingly accepted as a modality for evaluation of many malignancies. F-18 FDG however, can accumulate intensely in inflammatory lesions. Hence, tuberculous lymphadenopathy is a mimicker of lymphoma on PET / CT.

CASE REPORT

A 19-year-old female presented with fever of unknown cause for one month, without chills, night sweat, cough or stethocatharsis. Laboratory findings including CBC and tumor markers (CEA, CA19-9, AFP, NSE, CYFRA21-1) were in the normal range. Tuberculin test was negative. Contrast-enhanced thoracic CT scan revealed enlargement of lymph nodes in right neck, mediastinum and left hilum with heterogeneous contrast enhancement (Fig.1). The finding was suspicious of lymphoma. The patient was referred for a PET / CT scan. The scan showed increased FDG uptake of multiple lymph nodes in the root of neck of both sides, supraclavicular and postclavicular regions (SUVmax = 5.60), mediastinal and left hilar regions (SUVmax = 6.86). The spleen was slightly enlarged with mildly increased diffuse FDG uptake (SUVmax = 2.86, Fig. 2 - 4).

Four days later, right supraclavicular lymph node biopsy was performed. Microscopic examination showed central necrosis surrounded by lymphatic tissue and inflammatory cells. Staining for acid-fast bacilli was positive (Fig. 5).

Clinical, radiological, and pathological findings were consistent with the diagnosis of the tuberculous lymphadenopathy.

DISCUSSION

Non-invasive examinations, including X-ray, CT, tuberculin test, hematology test, routine sputum culture are used to diagnose the disease. However these tests could be negative.

Tuberculous lymphadenitis in neck or mediastinum is seen on CT as nodes with central low attenuation

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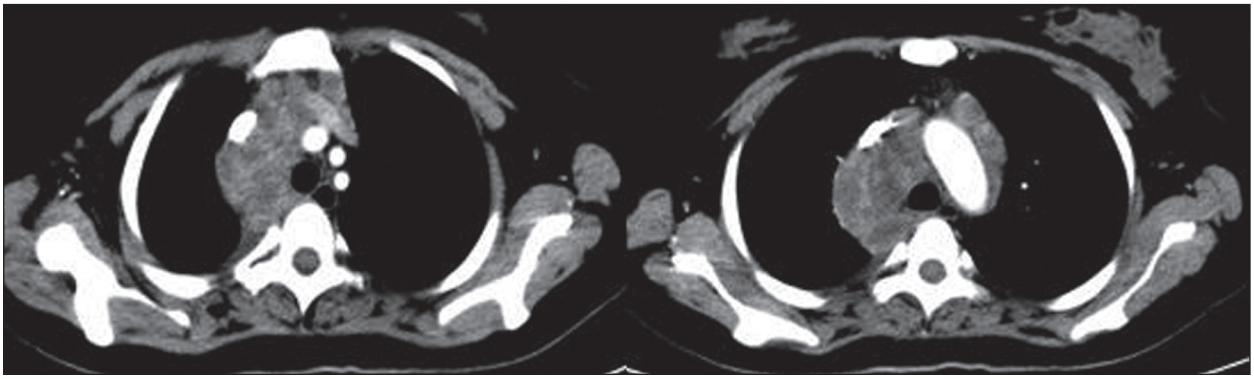

Fig. 1: Contrast-enhanced thoracic CT scan showing enlargement of lymph nodes in mediastinum with heterogeneous contrast enhancement

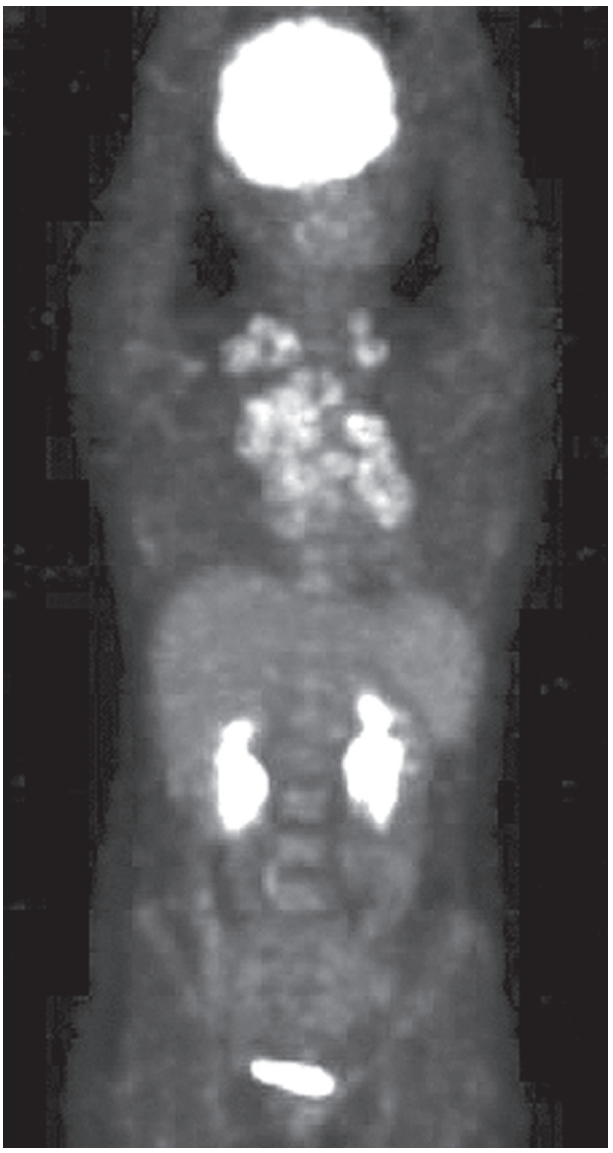

Fig. 2: Whole-body projection image in a 19-year-old female with fever of unknown etiology showing intense F-18 FDG uptake by multiple lymph nodes including root of neck on both sides, supraclavicular and postclavicular regions, mediastinal and left hilar regions

and peripheral rim enhancement or calcification. If present, these findings can be a strong indicator of the disease. However, the imaging features are varied and non-specific[1].

PET / CT is the most important recent advance in non-invasive lymphoma assessment. It has high sensitivity and specificity in patients with HL and most subtypes of indolent and aggressive NHL. Intense focal F-18 FDG uptake in widespread lymphadenopathy could be caused by lymphoma and other infectious diseases such as tuberculosis, especially in a region with a high prevalence of granulomatous disease[2,3]. The reason is that F-18 FDG accumulates in inflammatory cells such as neutrophils, lymphocytes, and activated macrophages and is seen *in vitro*[4]. Because of the high glucose utilization of inflammatory cells in granulomatous disease, false-positive FDG uptake in patients with tuberculosis should be expected[5-6]. Thus, the increased uptake in cervical lymph nodes on F-18 FDG PET / CT imaging should be diagnosed as tuberculous lymphadenitis, lymphoma or distant lymph node metastasis for the patient with tumors[7].

F-18 FDG PET can be associated with false-positive findings, especially in those with a high incidence of infectious disease. Our case did have pathological proof of tuberculous lymphadenitis. However, lymphadenopathy, especially in the region of cervical, mediastinal, left hilar and supraclavicular, region makes malignancy more likely. This case reminds us that for those patients presenting with intense F-18 FDG uptake of multiple lymph nodes on PET / CT, a differential diagnosis of lymphoma and granulomatous disease, such as tuberculosis should be warranted[8]. Then, it is beneficial for a patient's outcome or definitive treatment that we have a high index of suspicion and go for an early biopsy for histopathological diagnosis. We should remember that in PET / CT scan F-18FDG can also accumulate intensely in inflammatory lesions and can mimic lymphoma.

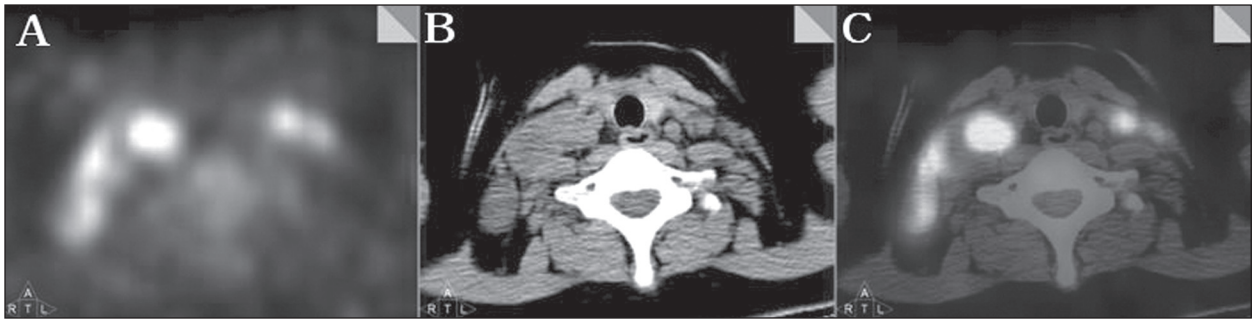

Fig. 3: Transverse slice of PET (a), CT (b) and PET / CT fusion image (c) showing intense F-18 FDG uptake of multiple lymph nodes in supraclavicular and postclavicular regions

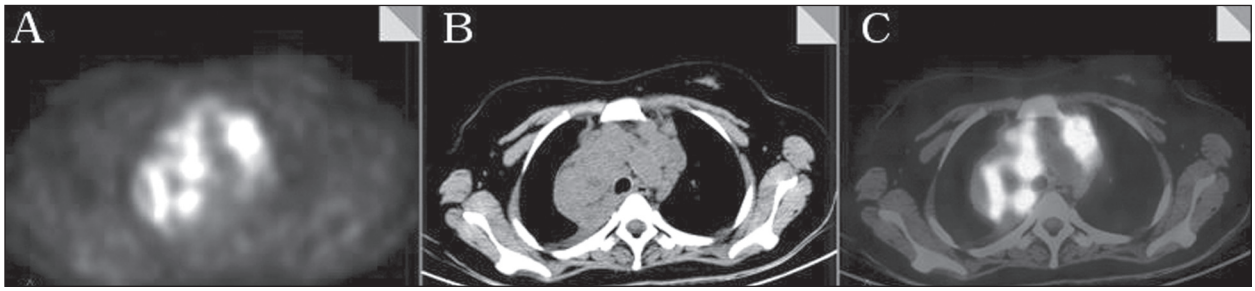

Fig. 4: Transverse slice of PET (a), CTm (b) and PET / CT fusion image (c) showing intense F-18 FDG uptake of multiple lymph nodes in mediastinal and left hilar regions

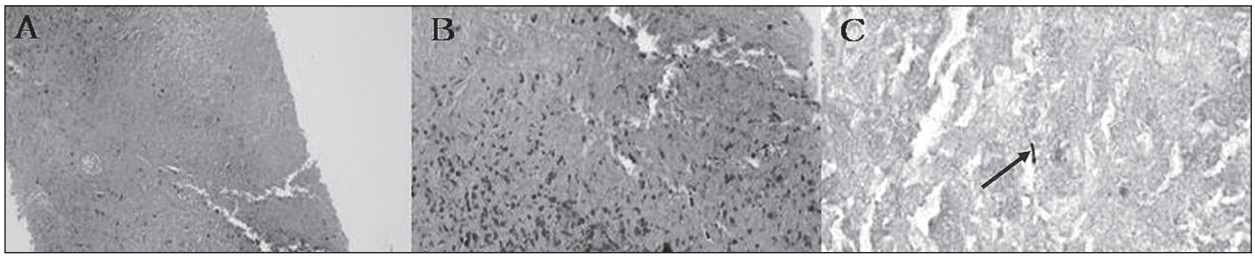

Fig. 5: Open biopsy of right supraclavicular lymph node shows central necrosis sourounded by lymphatic tissue and inflammatory cells (a) HE. Original magnification X 200; (b) HE. Original magnification X 400). Staining for acid-fast bacilli (c) Original magnification X 1000) finds a positive bacillus (arrow). These findings are typical in patients with tuberculous lymphadenitis.

CONCLUSION

This is a rare case of pulmonary tuberculous lymphadenopathy in an asymptomatic 19-year-old female. Her PET / CT scan demonstrated significant metabolic activity of the lymph nodes. She was diagnosed with tuberculous lymphadenopathy by histopathological examination.

ACKNOWLEDGMENT

Declaration: The first two authors contributed equally to this work.

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Letter to the Editor

Acute Acalculous Cholecystitis due to Leptospirosis

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Acute cholecystitis in the absence of any stones is defined as acute acalculous cholecystitis and has often been associated with severe illness or major surgeries in patients with significant co-morbid conditions. Infectious disease presenting as acute acalculous cholecystitis is rare. We report a case of leptospirosis presenting with acute acalculous cholecystitis as the initial manifestation.

A 45-year-old woman presented with a one-week history of fever, vomiting and abdominal pain. She was a housewife. There had been recent rainfall, and she had walked through this water or had recently sustained rain water on her eyes over the last one month. At the emergency service where she was initially evaluated, an abnormal examination result prompted a diagnosis of acute tonsillitis, and she had received five days of amoxicillin-clavulanate 2 x 625 mg / day as treatment prior to this admission. She took no other medications. Although she had used an antibiotic, there was no clinical response. On examination, she was well-built and nourished. She was alert but appeared ill, with fever (39 °C), a blood pressure of 120/70 mmHg and a pulse rate of 95 beats/minute. She had non-specific right upper quadrant tenderness. Otherwise, she was hemodynamically stable. Urine output was normal. Chest radiography was unremarkable.

Additional laboratory values during hospitalization were as follows: serum creatinine 0.8 mg/dl (normal 0.6 - 1.2 mg/dl), alanine aminotransferase 88 U/l (normal 10 - 40 U/l), aspartate aminotransferase 76 U/l (normal 10-40 U/l), total bilirubin 0.3 mg/dl (normal 0.1 - 1.2 mg/d), direct bilirubin 0.1 mg/d (normal < 0.3 mg/dl), alkaline phosphatase 154 U/l (normal 35 - 125 U/l), gama glutamyl transferase 125 U/l (normal 7 - 32 U/l) creatinine phosphokinase 304 U/l (0 – 145 U/l), white blood cell count 7,300/ mm^3 (5.000 – 10.000/ mm^3), and minimum platelet count 316,000/mm^3 (150,000 - 400,000/mm^3). Urine investigations showed hematuria, pyuria and proteinuria. Abdominal ultrasound showed mild hepatomegaly and pericholecystic collection. A clinical diagnosis of acute cholecystitis was made and ceftriaxone 2 x 1 g/day was administered. Viral hepatitis markers for hepatitis A, B and C were negative. Microscopic agglutination test (MAT) was also positive (titer 1:50) for *Leptospira icterohaemorrhagiae*. Her general condition and laboratory findings improved with 14 days of ceftriaxone treatment. She was discharged after two weeks of hospitalization.

Leptospirosis is a widespread zoonosis caused by a ubiquitous spirochete and commonly occurs after exposure to water or soil contaminated by infected animal urine, typically that of rats. It is common in developing countries and in areas where there is frequent contacts with contaminated water. Manifestations can be self-limiting (80 to 90%), presenting with fever, myalgia and malaise. Weil's disease, the fulminant form (5 to 10%) usually presents with kidney and liver involvement and is associated with significant morbidity and mortality (5 to 10%)[1]. Leptospirosis presenting as acute acalculous cholecystitis is rare[2-4]. Early diagnosis requires a high index of suspicion as presentation may be non-specific. Leptospirosis has been associated with elevated creatinine phosphokinase and it has been suggested that leptospirosis should be included in the differential diagnosis of acute

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acalculous cholecystitis of unknown etiology. In our case, the diagnosis was based on the strongly positive MAT, clinical features and laboratory investigations that were supportive of the diagnosis

In conclusion, our case highlights important manifestations of leptospirosis. Clinicians should consider leptospirosis as a differential diagnosis in patients presenting with acute acalculous cholecystitis, particularly if there are risk factors.

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Selected Abstracts of Articles Published Elsewhere by Authors in Kuwait

Kuwait Medical Journal 2013, 45 (1): 76 - 79

Primary Hydatid Cyst of the Supraspinatus Muscle: Complete Removal of the Germinal Layer and Cytodiagnosis by Fine-Needle Aspiration

Das DK, El-Sharawy M, Ayyash EH, Al-Enezi NA, Iqbal JR, Madda JP
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Diagn Cytopathol 2012 Sep 25. doi: 10.1002/dc.22925

Primary hydatid disease of the skeletal muscle without systemic involvement is rare. The purpose of this report is to document the novel clinical presentation and the interesting facets of fine-needle aspiration in a case of hydatid disease. It was a case of primary hydatid cyst of the left supraspinatus muscle in an Indian woman living in Kuwait, which was clinically diagnosed as a lipoma. Fine-needle aspiration (FNA) yielded 2 ml of clear fluid with white particulate material. The cytocentrifuged smears prepared from the aspirated fluid showed many scolices, occasional laminated cyst wall fragments and numerous hooklets. The laminated cyst wall and scolices were PAS positive. Trichrome staining imparted a demon-head-like appearance to the scolices. The cytodiagnosis of hydatid cyst was corroborated by histopathological examination of an excised whitish membrane and an irregular cystic fragment, which showed parallel laminations without germinal layer, and skeletal muscle with granulomas and a dense eosinophilic infiltration, respectively. Quantitative serological (indirect hemagglutination) test on blood sample collected 9 days after the excision of the cyst showed insignificant antibody titer to Echinococcus sp. and after 6 weeks the antibodies were completely absent. CT scan of the chest and abdomen performed 7 weeks after removal of cyst showed no evidence of visceral hydatid cyst.

Persistent Candidemia in Neonatal Care Units: Risk Factors and Clinical Significance

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Int J Infect Dis 2012 Dec 28. pii: S1201-9712(12)01313-6. doi: 10.1016/j.ijid.2012.11.020

Objectives: The prevalence and clinical significance of persistent candidemia among neonates are poorly understood. This study aimed to describe the rate and the clinical relevance of persistent candidemia over a 4-year period in Kuwait.
Methods: A retrospective chart review of infants admitted to the Neonatal Care Unit of the Maternity Hospital in Kuwait between January 2007 and December 2010, who had a positive blood culture for Candida species, was conducted. Persistent candidemia was defined as the isolation of the same Candida species more than 6 days after the initiation of antifungal therapy, or death due to candidemia within 6 days of antifungal treatment. Stepwise logistic regression was used to investigate factors associated with persistent candidemia.
Results: Of 89 neonates with a Candida infection, 54 (60.7%, 95% confidence interval 49.7-70.9%) had persistent candidemia. The case-fatality rate was 54% among those with persistent candidemia and 3% among those with non-persistent candidemia ($p<0.001$). Neonates with persistent candidemia were more

likely to be female, have a central vascular catheter at diagnosis, and have a low platelet count. All isolated Candida species were susceptible to antifungal agents.
Conclusions: Persistent candidemia is common among neonates with a Candida infection and is associated with an increased risk of mortality. Drug resistance is unlikely to explain the persistent candidemia; host-related factors seem to be more important and hence could be used to identify those at risk in order to institute appropriate preventive and treatment measures.

Diabetic Status of Patients with Leprosy in Kuwait

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Objective: The aim of this study was to screen for diabetes mellitus in leprosy patients to elucidate whether leprosy infection may play a role in the pathogenesis of diabetes mellitus in this population.
Subjects And Methods: Thirty patients of different ages and of both sexes with various types of leprosy were included in this study. In addition, 15 healthy individuals of comparable age and sex who had no family history of diabetes mellitus were identified as controls. In both groups, determinations of fasting and postprandial blood sugar, an oral glucose tolerance test (OGTT), measures of fasting serum insulin and pro-inflammatory cytokine tumor necrosis factor alpha (TNFα), as well as calculations using the Homeostasis Model Assessment for Insulin Resistance (HOMA-IR), were carried out.
Result: Approximately 13.3% of the leprosy patients were diabetic, and 37.7% were in pre-diabetic. The highest incidences of diabetes and pre-diabetes were in lepromatous leprosy (10% and 20%, respectively); a lower incidence of pre-diabetes (6.6%) was observed in tuberculoid leprosy; and the lowest incidence of diabetes (0.0%) was noted in borderline leprosy patients. Although normal healthy persons were not diabetic (0%), 20% were pre-diabetic.
Conclusion: This study revealed that the incidence of diabetes was higher in the leprosy patients than in the control group. As a result, we recommend that all leprosy patients should be screened for diabetes.

Caries Experience among Children with Type 1 Diabetes in Kuwait

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Pediatr Dent 2012; 34:468-472

Purpose: The purpose of this study was to determine the association among type 1 diabetes mellitus (DM), caries experience, and salivary glucose in 12- to 15-year-olds in Kuwait.
Methods: A cross-sectional design was chosen involving 53 DM patients and 53 nondiabetic controls, group-matched by age and sex to the experimental group. The DM patients comprised 2 groups: (1) 14 controlled DM children (glycated haemoglobin, HbA1c = <8); and (2) 39 children with uncontrolled DM (HbA1c >8). The children's caries experience, at the precavitation and cavitation diagnostic threshold, was measured. In addition, their frequency of sugar consumption, plaque index, salivary flow rate, buffering capacity, as well as mutans streptococci, lactobacilli, and yeast counts were recorded.
Results: The DM children had significantly higher caries experience both at precavitation and cavitation diagnostic thresholds, than the control group. Multiple logistic regression analysis showed age, frequency of sugar consumption, and resting salivary flow rate to be significantly associated with high caries experience among the diabetic children.
Conclusion: Caries experience was significantly higher in children with type 1 diabetes than in nondiabetic controls.

Prevalence of Low Bone Mass in Postmenopausal Kuwaiti Women Residents in the Largest Province of Kuwait

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Arch Osteoporos 2012; 7:147-53. doi: 10.1007/s11657-012-0092-1

We measured bone mineral density (BMD) in Kuwaiti women residents in the largest province of Kuwait state to highlight the BMD changes with each age, in particular when they reach the postmenopausal stage. Healthy Kuwaiti females between the ages of 10 and 89 years, who were residents in the largest province of Kuwait, were included in the study. After measurements of their height and weight, their bone mineral density of L2-L4 lumbar spine and femur (neck and total) was measured using dual-energy X-ray absorptiometry. Out of the studied 903 female subjects, 811 fulfilled the inclusion criteria. Their mean ± SEM age and body mass index (BMI) were respectively 47 ± 1 years and 30.8 ± 0.2 kg/m(2). Out of these 811 subjects, 454 were postmenopausal, and their age and BMI were 55.0 ± 0.3 years and 32.0 ± 0.3 kg/m(2), respectively. We have demonstrated that osteoporotic BMD of the spine and femur neck occurred in 20.2 and 12.5 % of postmenopausal Kuwaiti females, whereas osteopenic BMD of the spine and femur neck was observed at a frequency of 35.4 and 42.8 % of women, respectively. When the subjects were subdivided as per BMI, it was notable that overweight and obese had significantly higher BMD than normal weight postmenopausal women. BMD of the spine, femur neck, and femur total demonstrated significant positive correlations with body weight and BMI, whereas they demonstrated significant negative correlations with age. Low BMD of the femur neck and spine, reflected by the combination of osteopenia and osteoporosis, seemed to occur in more than half (55.3 - 55.6 %) of postmenopausal Kuwaiti women.

Objectives: Most of the studies on assessment of prevalence of low bone mass were focused in Caucasian population. Data on subjects of the Mediterranean area are limited. We measured bone mineral density (BMD) in Kuwaiti women residents in the largest province of Kuwait state to highlight the BMD changes with each age, in particular when they reach the postmenopausal stage.

Subjects and Methods: Kuwaiti female subjects of different age groups between 10 and 89 years, who were residents in the largest province of Kuwait (Hawalli), were included in the study. They were included if they had been healthy over the last 12 months, had no past history of bone disease, and are not taking any prescription medication that may affect bone density. Their bone mineral density of L2-L4 lumbar spine and femur (neck and total) was measured using dual-energy X-ray absorptiometry.

Results: Out of the studied 903 female subjects, 811 fulfilled the inclusion criteria and were included in the study. Their mean ± SEM age and body mass index (BMI) were respectively 47 ± 1 years and 30.8 ± 0.2 kg/m(2). Out of these 811 subjects, 454 were postmenopausal, and their age and BMI were 55.0 ± 0.3 years and 32.0 ± 0.3 kg/m(2), respectively. We have demonstrated that osteoporotic BMD of the spine and femur neck occurred in 20.2 and 12.5 % of postmenopausal Kuwaiti females, respectively, whereas osteopenic BMD of the spine and femur neck was observed at a frequency of 35.4 and 42.8 % of women. When subjects were subdivided as per BMI, it was notable that overweight and obese postmenopausal women had significantly higher BMD of lumbar spine, femur neck, and femur total than normal weight postmenopausal women. Bone mineral densities of the spine, femur neck, and femur total demonstrated significant positive correlations with body weight and BMI, whereas they demonstrated significant negative correlations with age.

Conclusion: Low BMD of the femur neck and spine, reflected by the combination of osteopenia and osteoporosis, seemed to occur in more than half (55.3-55.6 %) of postmenopausal Kuwaiti women residents at the largest province of Kuwait.

Impact of Pneumococcal Conjugate Vaccines on Burden of Invasive Pneumococcal Disease and Serotype Distribution of *Streptococcus Pneumoniae* Isolates: An Overview from Kuwait

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Diseases caused by *Streptococcus pneumoniae* are a major worldwide public health problem. The seven-valent pneumococcal conjugate vaccine (PCV7) was introduced in Kuwait in August 2006 and the 13-valent vaccine, PCV13, in August 2010, for children aged <2 years, with catch-up programs for those from 2 to 5 years. The objective of this study was to evaluate the impact of vaccination on vaccine and non-vaccine serotype distribution in invasive and noninvasive *S. pneumoniae* isolates obtained in Kuwait from August 2006 through December 2011, as compared with previously published data. The susceptibility of all the isolates to penicillin was also evaluated. The study included all cases of noninvasive and invasive pneumococcal diseases (IPD) in children and adults among all age groups during this period. All isolates were serotyped using the Quellung reaction antisera and their susceptibility to penicillin was determined using the E test method. A total of 395 pneumococcal isolates were included in the study. After vaccine introduction, 23% of isolates were from children ≤ 5 years of age and 49% of cases in this age group were invasive, while 46% of isolates were from adults > 50 years of age and 27% of cases in this age group were invasive. Two of 13 cerebrospinal fluid isolates and only one of 266 respiratory isolates obtained were penicillin resistant. For the post-vaccine period, the predominant serotypes in children ≤ 5 years were 19F, 19A, 6A, 8 and 15B for invasive isolates and 19F and 23F for noninvasive isolates and the predominant serotypes in adults > 50 years of age were 14, 3, 1, 19F and 8 for invasive isolates and 19F, 23F, 6B, 14 and 19A for noninvasive isolates. Among children < 2 years of age, coverage with PCV7, PCV10, and PCV13 was 34.6%, 38.5% and 61.5%, respectively, in the period post-vaccine introduction. Among children 2 - 5 years of age, corresponding coverage rates were 42.1%, 47.4% and 63.1%, respectively. A similar trend was noticed in adults, with coverage rates in the 51- to 65 - years age group of 45.8%, 62.5% and 70.8% respectively. Compared with previously published findings, from the period prior to vaccine introduction, this represented an increased incidence in some non-PCV7 serotypes that are included in PCV13 (serotypes 1, 6A, and 3). In conclusion, with the emergence of new pneumococcal serotypes, broader vaccine coverage will aid in the prevention of IPD in children.

Forthcoming Conferences and Meetings

Compiled and edited by
Babichan K Chandy

Kuwait Medical Journal 2013; 45 (1): 80 - 86

Specialty Skills in **Coloproctology** Stage 2 (St6-8)
Mar 21 - 22, 2013
United Kingdom / London
Contact: Royal College of Surgeons of England
Tel: 011-44-20-7869-6300
Email: education@rcseng.ac.uk

Adult Infectious Diseases: Evidence based primary prevention and treatment
Mar 25 - 27, 2013
United States / California / Anaheim
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Tel: 888-533-9031; Fax: 858-777-5588
Email: info@mceconferences.com

Thyroid and Parathyroid Masterclass
Mar 25, 2013
United Kingdom / London
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Email: education@rcseng.ac.uk

17th Pan Arab Conference on **Diabetes**
Mar 26 - 29, 2013
Egypt / Cairo
Contact: Conference Secretariat, Pure Spot Congress and Event Organizers
Tel: 011-20-2-2672-1944; Fax: 011-20-2-2671-8421
Email: pure@onlinediabetes.net

Head and Neck surgical anatomy: **'Hands On' Cadaver** workshop
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United Kingdom / York
Contact: Hull York Medical School
Email: postgraduate@hyms.ac.uk

7th Middle East **Cardiovascular** conference: MECC 2013
Mar 30 - Apr 2, 2013
Turkey / Istanbul
Website: http://www.mecc.ir/

Nuclear Receptors & Friends: Roles in energy homeostasis & metabolic dysfunction
Apr 3 - 8, 2013
Austria / Alpbach
Contact: Keystone symposia on molecular and cellular biology
Tel: 800-253-0685 or 970-262-1230; Fax: 970-262-1525
Email: info@keystonesymposia.org

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United Kingdom / London
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Controversies in **Rheumatology & Autoimmunity** 2013
Apr 4 - 6, 2013
Hungary / Budapest
Contact: Ronit Eisenbach, APM, Kenes International
Tel: 011-41-22-908-0488; Fax: 011-41-22-906-9140
Email: cora@kenes.com

Society for **Emergency Medicine** in Singapore annual scientific meeting 2013
Apr 6 - 7, 2013
Singapore / Singapore
Contact: SEMS ASM 2013 , Society for emergency medicine in Singapore
Email: semsasm2013@gmail.com

Intermediate Skills in **Laparoscopic Surgery**
Apr 9 - 10, 2013
United Kingdom / London
Contact: Royal College of Surgeons of England
Tel: 011-44-20-7869-6300
Email: education@rcseng.ac.uk

7th world congress on controversies in **Neurology** (CONY)
Apr 11 - 14, 2013
Turkey / Istanbul
Contact: Congress Secretariat, ComtecMED
Tel: 011-972-3-566-6166; Fax: 011-972-3-566-6177
Email: cony@comtecmed.com

Advances in **Diabetes and Insulin Therapy** - Adit 2013
Apr 11 - 14, 2013
Bulgaria / Sofia
Contact: Rok Bolcina, Registration and Housing Manager, POTNIK d.o.o.
Email: info@adit-conf.org

Annual paediatric update conference 2013: Operative skills in **Neurosurgery**
Apr 17 - 19, 2013
United Kingdom / London
Contact: Royal College of Surgeons of England
Tel: 011-44-20-7869-6300
Email: education@rcseng.ac.uk

2013 world congress on **Osteoarthritis**
Apr 18 - 21, 2013
United States / Pennsylvania / Philadelphia
Contact: Annemarie Kehler, Meeting & Registration Coordinator, Osteoarthritis Research Society International
Tel: 856-642-4429; Fax: 856-439-0525
Email: akehler@oarsi.org

5th Pan Arab Congress of **Sexual Health**
Apr 18 - 20, 2013
United Arab Emirates / Dubai
Contact: Adel Zakaria, Congress Organizer, Charisma Travel
Tel: 011-21-2-2216-3858; Fax: 011-20-2-2418-4645
Email: mohamedtarekanis@gmail.com

Comprehensive **Colposcopy**
Apr 18 - 21, 2013
United States / Georgia / Atlanta
Contact: American Society for Colposcopy and Cervical Pathology
Tel: 301-733-3640; Fax: 301-733-5775

Update in **General Surgery** 2013
Apr 18 - 20, 2013
Ontario / Toronto
Contact: Continuing Education and Professional Development, University of Toronto
Tel: 416-978-2719
Email: info-sur1304@cepdtoronto.ca

Musculoskeletal Ultrasound course for rheumatologists - fundamentals
Apr 20 - 21, 2013
United States / Illinois / Chicago
Contact: American College of Rheumatology
Tel: 800-636-4766 (US & Canada) or 415-979-2265; Fax: 415-293-5231
Email: ACRProfMtgs@cmrus.com

Nephrology 2013
Apr 21 - 26, 2013
United States / Massachusetts / Boston
Contact: Harvard Medical School, Department of Continuing Education, Agri Meetings
Tel: 617-384-8600
Email: hms-cme@hms.harvard.edu

14th International workshop on **Clinical Pharmacology of HIV Therapy**
Apr 22 - 24, 2013
United Kingdom / Liverpool
Contact: Wilco Keulen, Virology Education B.V
Tel: 011-31-30-230-7140; Fax: 011-31-30-230-7148
Email: wilco.keulen@vironet.com

1st International **Pediatric Psycho-Oncology** workshop
Apr 22 - 25, 2013
Egypt / Cairo
Contact: Dr. Mohammad ElShami, Director of the psychiatric department, Children Cancer Hospital Egypt 57357
Tel: 011-20-2-2535-1500
Email: mohammad.elshami@57357.com

Hot Topics in **Anesthesia + ACLS + NRP + PALS**
Apr 22 - 25, 2013
United States / Nevada / Las Vegas
Contact: Northwest Anesthesia Seminars, Inc.
Tel: 509-547-7065; Fax: 509-547-1265
Email: info@nwas.com

Malaria Vaccines for the world
Apr 22 - 24, 2013
Switzerland / Lausann
Contact: John Herriot, Meetings Management
Tel: 011-44-1483-427-440; Fax: 011-44-1483-428-516
Email: jherriot@meetingsmgmt.u-net.com

Angioplasty Summit TCTAP 2013
Apr 23 - 26, 2013
South Korea / Seoul
Contact: Harim Jin, Summit MD
Email: cvrf@summitmd.com

34th Annual advances in **Infectious Diseases**: New directions for primary care
Apr 24 - 26, 2013
United States / California / San Francisco
Contact: Office of Continuing Medical Education, UCSF CME Registration Office
Tel: 415-476-5808; Fax: 415-502-1795
Email: info@ocme.ucsf.edu

International Society for **Heart & Lung Transplantation** (ISHLT) 33rd annual meeting & scientific sessions
Apr 24 - 27, 2013
Canada, Quebec / Montreal
Contact: ISHLT
Tel: 972-490-9495; Fax: 972-490-9499
Email: meetings@ishlt.org

Bit's 4th Annual World **DNA and Genome** Day (WDD-2013)
Apr 25 - 27, 2013
China / Nanjing
Contact: Jessica Tong , WDD-2013, BIT Congress, Inc.
Tel: 011-86-411-8479-9609 ext. 801; Fax: 011-86-411-8479-9629
Email: Jessica@dnaday.com

Geriatric medicine
Apr 25 - 27, 2013
New Mexico / Albuquerque
Contact: American Academy of Family Physicians
Tel: 800-274-2237 or 913-906-6000; Fax: 913-906-6075

43rd Annual **Aesthetic Plastic Surgery** symposium 2013
Apr 26 - 27
Canada, Ontario / Toronto
Contact: Continuing Education and Professional Development, University of Toronto
Tel: 416-978-2719
Email: info.cepd@utoronto.ca

23rd European Congress of **Clinical Microbiology and Infectious Diseases**
Apr 27 - 30, 2013
Germany / Berlin
Contact: Congrex Switzerland Ltd.
Tel: 011-41-61-686-7777; Fax: 011-41-61-686-7788
Email: basel@congrex.com

5th International Conference: Advances in **Orthopaedic Osseointegration**
May 1 - 31, 2013
Sweden / Gothenburg
Contact: Office of Continuing Medical Education, UCSF CME Registration Office
Tel: 415-476-5808; Fax: 415-502-1795
Email: info@ocme.ucsf.edu

Arteriosclerosis, Thrombosis & Vascular Biology (ATVB) 2013 scientific sessions
May 1 – 3, 2013
United States / Florida
Contact: American Heart Association
Tel: 888-242-2453
Email: scientificconferences@heart.org

Definitive **Surgical Trauma** skills (DSTS)
May 1 – 2, 2013
United Kingdom / London
Contact: Royal College of Surgeons of England
Tel: 011-44-20-7869-6300
Email: education@rcseng.ac.uk

2013 Annual Paris **Melanoma** conference
May 2 – 3, 2013
France / Paris
Contact: Elise van Spijke, Project Manager, Prime Oncology
Tel: 011-31-70-306-7190; Fax: 011-31-70-331-8335
Email: ParisMelanoma2013@prIMEoncology.org

Basic **Surgical Anatomy of the Head and Neck**
May 2 – 3, 2013
United Kingdom / London
Contact: Royal College of Surgeons of England
Tel: 011-44-20-7869-6300
Email: education@rcseng.ac.uk

Female **Pelvic Medicine & Reconstructive Surgery** Update 2013
May 2 – 4, 2013
United States / Texas / Austin
Contact: American Urogynecologic Society
Tel: 202-367-1167; Fax: 202-367-2167
Email: info@augs.org

Focused **Thoracic and Vascular Ultrasound**
May 2 – 3, 2013
United States / Illinois / Northbrook
Contact: American College of Chest Physicians
Tel: 847-498-1400; Fax: 847-498-5460

15th Annual Update in **Infectious Diseases**
May - 2, 2013
United States / Iowa
Contact: Carver College of Medicine, University of Iowa
Tel: 319-335-8599

Ultrasound Guided **Regional Anesthesia & Vascular Access** Workshop
May - 3, 2013
United States / California
Contact: Northwest Anesthesia Seminars, Inc.
Tel: 509-547-7065; Fax: 509-547-1265
Email: info@nwas.com

Percutaneous Tracheostomy Under Endoscopic Control
May - 7, 2013
United Kingdom / Dundee
Contact: Susan McComiskie, Course Secretary, Cuschieri Skills Centre University of Dundee
Tel: 011-44-13-8238-3400; Fax: 011-44-13-8264-6042
Email: s.mccomiskie@dundee.ac.uk

Advanced **Airways Techniques** Course
May - 8, 2013
United Kingdom / Dundee
Contact: Susan McComiskie, Course Secretary , Cuschieri Skills Centre
Tel: 011-44-13-8238-3400; Fax: 011-44-13-8264-6042
Email: s.mccomiskie@dundee.ac.uk

Advances in **Rhinoplasty** 2013
May 8 - 11, 2013
United States / Illinois
Contact: American Academy of Facial Plastic and Reconstructive Surgery Foundation
Tel: 703-299-9291; Fax: 703-299-8898
Email: info@aafprs.org

International investigative **Dermatology** 2013
May 8 - 11, 2013
United Kingdom / Edinburgh
Contact: Conference & Event Services, IID 2013
Tel: 011-44-20-7391-6357; Fax: 011-44-20-7388-0487
Email: iid2013@bad.org.uk

Specialty Skills in **Oncoplastic and Breast Reconstruction Surgery** Level II
May 8 - 9, 2013
United Kingdom / London Oncology
Contact: Royal College of Surgeons of England
Tel: 011-44-20-7869-6300
Email: education@rcseng.ac.uk

Transcranial Doppler Course
May 8 - 10, 2013
United States / California
Contact: Karen Einstein, Office of Continuing Medical Education , UC Los Angeles
Tel: 310-206-0626
Website: http://www.cme.ucla.edu/courses/event-description?event_id=2075559

Facial Aesthetic / Occuloplastic Surgery & Rhinoplasty
May 10 - 13, 2013
United Kingdom / Coventry
Contact: Rachel Davies, Course Co-Ordinator, University hospitals Coventry and Warwickshire
Tel: 011-44-24-7696-8722; Fax: 011-44-24-7696-8715
Email: Rachel.Davies2@uhcw.nhs.uk

Virtual **Colonography**
May 13 - 15, 2013
Canada / Ontario
Contact: Gina Sciortino Administrative Assistant, University of Toronto
Tel: 416-340-4800 ext. 5439
Email: gina.sciortino@uhn.ca

Intermediate **Thoracic Surgery**
May 14 - 15, 2013
United Kingdom / London
Contact: Royal College of Surgeons of England
Tel: 011-44-20-7869-6300
Email: education@rcseng.ac.uk

8th Medical Update for the **Psychiatrist**
May 15 - 16, 2013
United Kingdom / London Psychiatry
Contact: Luis G Macchiavello, Director, Infomed Research and Training
Tel: 011-44-20-8123-0021; Fax: 011-44-20-8290-6917
Email: courses@infomedltd.co.uk

Pediatric Colorectal Problems
May 15 - 17, 2013
United States / Ohio
Contact: Cincinnati Children's Hospital Medical Center
Tel: 513-636-4200
Website:http://www.cincinnatichildrens.org/professional/continuing-education/cme/ce-calendar/

Stroke Symposium
May - 15, 2013
United States / Nebraska
Contact: Continuing Medical Education Division, Creighton University Medical Center School of Medicine
Tel: 402-280-1830
Website: http://medschool.creighton.edu/?id=2636

5th Baltic Congress of **Ophthalmology**
May 15 - 20, 2013
Germany / Kiel
Contact: Frau C. Seitz, Augenklinik Bellevue
Tel: 011-49-431-20108-4444
Email: c.seitz@augenklinik-bellevue.de

Carotid Ultrasound Imaging
May - 18, 2013
United Kingdom / London
Contact: Secretariat , Wessex Scientific
Fax: 011-44-13-8435-0132
Email: info@wessexscientific.com

26th International symposium on **Cerebral Blood Flow & Metabolism**/11th International conference on quantification of brain function with pet
May 20 - 23, 2013
China / Shanghai
Contact: Miriam Feeley, APM, Kenes International
Tel: 011-41-22-908-0488; Fax: 011-41-22-906-9140
Email: brain@kenes.com

2nd Asia Pacific **Behavioural and Addictions Medicine** Conference
May 20 - 23, 2013
Singapore / Singapore
Contact: Angie Ong, Ms , Ace Daytons Direct International Pte Ltd
Tel: 011-65-6379-5267; Fax: 011-65-6475-2077
Email: admin@apbam.org

Association of **Breast Surgery** 2013 Conference & Agm
May 21 - 22, 2013
United Kingdom / Manchester
Contact: Jackie Spencer-Smith, Association of Breast Surgery
Tel: 011-44-20-7869-6853
Email: jackiespencersmith@absgbi.org.uk

1st Global Conference on **Contraception, Reproductive and Sexual Health**
May 22 - 25, 2013
Denmark / Copenhagen
Contact: Nancy Habils, Ms, ESC Central Office
Tel: 011-32-2-582-0852; Fax: 011-32-2-582-5515
Email: congress@contraception-esc.com

Obstetric Anaesthesia 2013
May 22 - 24, 2013
United Kingdom / Bournemouth
Contact: OAA Secretariat, Obstetric Anaesthetists' Association
Tel: 011-44-20-8741-1311; Fax: 011-44-20-8741-0611
Website: http://www.oaa-anaes.ac.uk/content.asp?ContentID=492

Stem Cell & Regenerative Medicine
May 22 - 24, 2013
United States / California
Contact: Kristin Kozub, Marketing Manager , ACI
Tel: 312-780-0700
Email: kkozub@acius.net

Allergy and Asthma 2013
May 23 - 24, 2013
Belgium / Bruges
Contact: Abcam plc
Tel: 877-749-8807
Email: events@abcam.com

Bit's 6th Anniversary of **World Cancer Congress** (WCC-2013)
May 23 - 25, 2013
China / Xian
Contact: Nancy, BIT Congress, Inc.
Tel: 011-86-411-8457-5669 ext. 857
Fax: 011-86-411-8479-9629
Email: nancy@wcc-congress.com

European School of Interventional Radiology Course on **Biopsies & Drainage Procedures**
May 23 - 25, 2013
Turkey / Ankara
Contact: Ms. Verena Rath, ESIR Education Programmes
Email: office@esir.org

Infectious Disease Review
May 24 - 31, 2013
United Kingdom / Southampton
Contact: Continuing Education, Inc, Meeting Planner , Continuing Education, Inc.
Tel: 800-422-0711 or 727-526-1571; Fax: 727-522-8304
Email: contactus@continuingeducation.net

Certificate of **Skin Cancer** Medicine
May 25 - 26, 2013
Australia / Sydney Dermatology
Contact: Skin Cancer College Australasia
Email: info@skincancercollege.org

18th International Congress of **Cytology**
May 26 - 30, 2013
France / Paris
Contact: Organising Secretariat , 18th International Congress of Cytology
Tel: 011-33-1-5385-8275; Fax: 011-33-1-5385-8283
Email: info@cytologyparis2013.com

6th International Symposium on **Focal Therapy** & Imaging of Prostate & Kidney Cancer
May 29 - 31, 2013
Netherlands / Amsterdam
Contact: Vicky Nickolopoulou , Erasmus SA
Tel: 011-30-210-741-4718
Email: v.nickolopoulou@erasmus.gr

1st World Congress on **Pelvic Pain**
May 30 – Jun 1, 2013
Netherlands / Amsterdam
Contact: Congress Secretariat, Congress Consultants
Tel: 011-31-26-389-0680; Fax: 011-31-26-389-0686
Email: s.debruin@congressconsultants.com

3rd International Congress on **Neurobiology, Psychopharmacology** & Treatment Guidance
May 30 - Jun 2, 2013
Greece / Thessaloniki
Contact: Congress Secretariat, Global Events
Tel: 011-30-23-1024-7743; Fax: 011-30-23-1024-7746
Email: info@globalevents.gr

9th International Workshop on **Hiv & Hepatitis** Co-Infection
May 30 - 31, 2013
Italy / Rome
Contact: Wilco Keulen, Virology Education B.V.
Tel: 011-31-30-230-7140; Fax: 011-31-30-230-7148
Email: wilco.keulen@vironet.com

Advanced **Critical Care Echocardiography**
May 30 - Jun 2, 2013
United States / Illinois
Contact: American College of Chest Physicians
Tel: 847-498-1400; Fax: 847-498-5460
Website: http://www.chestnet.org/accp/events/advanced-critical-care-echocardiography

ISN World Congress of **Nephrology**
May 30 - Jun 4, 2013
China / Hong Kong
Contact: Jesper Lillelund, Marketing & Communications Director, International Society of Nephrology
Tel: 011-32-2-808-0420
Email: jlillelund@theisn.org

Toxicology
Jun 1, 2013
Canada / British Columbia
Contact: Gail Chapman, CME Coordinator , Canadian Association of Emergency Physicians
Tel: 613-523-3343 ext. 13; Fax: 613-523-0190
Email: gchapman@caep.ca

North American Masterclass in **Endoscopic Sinus** Surgery
Jun 5 - 7, 2013
Canada / Quebec
Contact: Gaby Stanischewski, McGill University
Tel: 514-843-2820
Email: gaby.stanischewski@muhc.mcgill.ca

Antepartum and Intrapartum Management
Jun 6 - 8, 2013
United States / California
Contact: Office of Continuing Medical Education, UCSF CME Registration Of?ce
Tel: 415-476-5808; Fax: 415-502-1795
Email: info@ocme.ucsf.edu

Challenges in **Gynecology**
Jun 6 - 8, 2013
United States / Nevada
Contact: Symposia Medicus
Tel: 800-327-3161 or 925-969-1789; Fax: 925-969-1795
Website: http://symposiamedicus.org/Conferences.aspx

Gastroenterology Training Course Summer School
Jun 6 - 9, 2013
Czech Republic / Prague
Contact: Wilma Hofer, UEG National Societies Committee
Tel: 011-43-1-997-1639; Fax: 011-43-1-997-1639 ext. 10
Email: w.hofer@medadvice.co.at

Virtual **Colonoscopy** Workshop
Jun 6 - 8, 2013
United States / California
Contact: Office of Continuing Medical Education, University of California, San Francisco
Tel: 415-476-4251; Fax: 415-476-0318
Email: info@ocme.ucsf.edu

Vascular Anomalies: A Clinical Approach
Jun - 7, 2013
United Kingdom / London
Contact: Miss Cristina Lai, Events Coordinator, University College London
Tel: 011-44-20-7905-2204
Email: cristina.lai@ucl.ac.uk

Liver Tumors: New Technologies and New Managements
Jun 8 - 9, 2013
United States / California
Contact: Cedars-Sinai Medical Center
Tel: 310-423-5548; Fax: 310-423-0309
Website: http://www.regonline.com/builder/site/Default.aspx?EventID=1164592

8th Asia Pacific Conference on **Clinical Nutrition**
Jun 9 - 12, 2013
Japan / Tokyo
Contact: Piyawan Bannasateinsri, APM, Kenes Asia
Tel: 011-66-2-748-7881; Fax: 011-66-2-748-7880
Email: apccn2013@kenes.com

2nd International Conference on **Gastroenterology & Urology**
Jun 10 - 12, 2013
United States / Illinois
Contact: Conference Secretariat, OMICS Group Conferences
Tel: 800-216-6499 (USA & Canada) l 1-800-651-097 (Australia) l 0805-080048 (Europe); Fax: 650-618-1414
Email: gastroenterology2013@omicsonline.com

Cardiac CT
Jun 10 - 14, 2013
Canada / Ontario
Contact: Gina Sciortino, Administrative Assistant, University of Toronto
Tel: 416-340-4800 ext. 5439
Email: gina.sciortino@uhn.ca

Diploma in **Occupational Medicine**
Jun 10 to Jul. - 26, 2013
United Kingdom / Birmingham
Contact: CPD Training Team, Institute of Occupational and Environmental Medicine , University of Birmingham
Tel: 011-44-12-1414-6013 / 6014
Fax: 011-44-12-1414-6217
Email: occhealth@contacts.bham.ac.uk

Management of **DVT and Pulmonary Embolism** Within Primary Care
Jun 10 - 11, 2013
United Kingdom / Birmingham
Contact: Tamara Ball, Centre for Professional Development , University of Birmingham
Tel: 011-44-12-1414-3281
Email: t.c.ball@bham.ac.uk

New Avenues for **Brain Repair**: Programming & Reprogramming the Central Nervous System
Jun 10 - 11, 2013
United States / Massachusetts
Contact: Abcam plc
Tel: 877-749-8807
Email: events@abcam.com

Core Skills in **Hand Surgery**
Jun 11 - 13, 2013
United Kingdom / London
Contact: Royal College of Surgeons of England
Tel: 011-44-20-7869-6300
Email: education@rcseng.ac.uk

Basic **Colposcopy**
Jun 12 - 13, 2013
United Kingdom / London
Contact: Royal College of Obstetricians and Gynaecologists
Email: events@rcog.org.uk

Transcatheter Valve Therapies (TVT) 2013
Jun 12 - 15, 2013
Canada / British Columbia
Contact: Cardiovascular Research Foundation
Tel: 646-434-4500
Email: info@crf.org

2013 Amsterdam **Foot & Ankle** Course
Jun 13 - 14, 2013
Netherlands / Amsterdam
Contact: Amsterdam Foot & Ankle Platform
Email: info@ankleplatform.com

9th Annual Advanced Learning In **Palliative Medicine** Conference
Jun 13 - 15, 2013
Canada / British Columbia
Contact: Division of Continuing Professional Development, University of British Columbia
Tel: 604-875-5101; Fax: 604-875-5078
Email: cpd.info@ubc.ca

Mammograms to Mri: **Breast Imaging and Interventions** 2013
Jun 16 - 19, 2013
United States / South Carolina
Contact: Debbie Griffin, Department of Radiology , Duke University School of Medicine
Email: deborah.griffin@duke.edu

World **Vaccine Congress Asia** 2013
Jun17 - 20 2013
Singapore
Contact person: Jolene Lee
Website: http://www.terrapinn.com/2013/world-vaccines-congress-asia/index.stm

Anticoagulation Management in Primary Care
Jun 17 - 19, 2013
United Kingdom / Birmingham
Contact: Amy Partleton, Centre for Professional Development, University of Birmingham
Tel: 011-44-12-1414-2677; Email: a.partleton@bham.ac.uk

Family Medicine: A Review and Update of Common Clinical Problems
Jun 17 - 21, 2013
United States / Florida
Contact: Trish or Tara, American Medical Seminars, Inc.
Tel: 866-267-4263 or 941-388-1766; Fax: 941-365-7073
Email: tkeeton@ams4cme.com

13th International Conference of **Forensic Mental Health** Services
Jun 18 - 21, 2013
Netherlands / Maastricht
Contact: International Association of Forensic Mental Health Services
Tel: 604-924-5026; Fax: 604-924-5027
Email: tmoropito@iafmhs.org

International Congress of **Toxicology** 2013
June 30 - July 4 2013
Korea (south) / Seoul
Contact person: Jessie Yoon
Website: http://www.ict2013seoul.org

International Congress on **Neurotechnology, Electronics and Informatics** (NEUROTECHNIX 2013)
Sep 19 – 21, 2013
Portugal / Vilamoura
Contact person: NEUROTECHNIX Secretariat
Website: http://www.neurotechnix.org

4th International Conference on **Stem Cells and Cancer** (ICSCC-2013): Proliferation, Differentiation and Apoptosis
Oct 19 - 22, 2013
India/ Mumbai, Maharashtra
Contact person: Prof. Dr. Sheo Mohan Singh
Website: http://www.icscc.in/

WHO-Facts Sheet

1. Measles
2. Pneumonia
3. Hepatitis B
4. Obesity and Overweight
5. Soil-Transmitted Helminth Infections

Compiled and edited by
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Kuwait Medical Journal 2013, 45 (1): 87 - 94

MEASLES

Overview

Measles is a highly contagious, serious disease caused by a virus. In 1980, before widespread vaccination, measles caused an estimated 2.6 million deaths each year. It remains one of the leading causes of death among young children globally, despite the availability of a safe and effective vaccine. An estimated 158,000 people died from measles in 2011 – mostly children under the age of five.

Measles is caused by a virus in the paramyxovirus family. The measles virus normally grows in the cells that line the back of the throat and lungs. Measles is a human disease and is not known to occur in animals.

Accelerated immunization activities have had a major impact on reducing measles deaths. Since 2000, more than one billion children in high risk countries were vaccinated against the disease through mass vaccination campaigns - about 225 million of them in 2011. Global measles deaths have decreased by 71% from 542,000 in 2000 to 158,000 in 2011.

KEY FACTS

- Measles is one of the leading causes of death among young children even though a safe and cost-effective vaccine is available.
- In 2011, there were 158,000 measles deaths globally – about 430 deaths every day or 18 deaths every hour.
- More than 95% of measles deaths occur in low-income countries with weak health infrastructures.
- Measles vaccination resulted in a 71% drop in measles deaths between 2000 and 2011 worldwide.
- In 2011, about 84% of the world's children received one dose of measles vaccine by their first birthday through routine health services – up from 72% in 2000.

Signs and symptoms

The first sign of measles is usually a high fever, which begins about 10 to 12 days after exposure to the virus, and lasts four to seven days. A runny nose, a cough, red and watery eyes, and small white spots inside the cheeks can develop in the initial stage. After several days, a rash erupts, usually on the face and upper neck. Over about three days, the rash spreads, eventually reaching the hands and feet. The rash lasts for five to six days, and then fades. On average, the rash occurs 14 days after exposure to the virus (within a range of seven to 18 days).

Severe measles is more likely among poorly nourished young children, especially those with insufficient vitamin A, or whose immune systems have been weakened by HIV / AIDS or other diseases.

Most measles-related deaths are caused by complications associated with the disease. Complications are more common in children under the age of five, or adults over the age of 20. The most serious complications include blindness, encephalitis (an infection that causes brain swelling), severe diarrhea and related dehydration, ear infections, or severe respiratory infections such as pneumonia. As high as 10% of measles cases result in death among populations with high levels of malnutrition and a lack of adequate health care. Women infected while pregnant are also at risk of severe complications and the pregnancy may end in miscarriage or preterm delivery. People who recover from measles are immune for the rest of their lives.

Address correspondence to:
Office of the Spokesperson, WHO, Geneva. Tel.: (+41 22) 791 2599; Fax (+41 22) 791 4858; Email: inf@who.int; Web site: http://www.who.int/

Who is at risk?

Unvaccinated young children are at highest risk of measles and its complications, including death. Unvaccinated pregnant women are also at risk. Any non-immune person (who has not been vaccinated or was vaccinated but did not develop immunity) can become infected.

Measles is still common in many developing countries – particularly in parts of Africa and Asia. More than 20 million people are affected by measles each year. The overwhelming majority (more than 95%) of measles deaths occur in countries with low per capita incomes and weak health infrastructures.

Measles outbreaks can be particularly deadly in countries experiencing or recovering from a natural disaster or conflict. Damage to health infrastructure and health services interrupts routine immunization, and overcrowding in residential camps greatly increases the risk of infection.

Transmission

The highly contagious virus is spread by coughing and sneezing, close personal contact or direct contact with infected nasal or throat secretions.

The virus remains active and contagious in the air or on infected surfaces for up to two hours. It can be transmitted by an infected person from four days prior to the onset of the rash to four days after the rash erupts.

Measles outbreaks can result in epidemics that cause many deaths, especially among young, malnourished children. In countries where measles has been largely eliminated, cases imported from other countries remain an important source of infection.

Treatment

No specific antiviral treatment exists for measles virus.

Severe complications from measles can be avoided through supportive care that ensures good nutrition, adequate fluid intake and treatment of dehydration with WHO-recommended oral rehydration solution. This solution replaces fluids and other essential elements that are lost through diarrhea or vomiting. Antibiotics should be prescribed to treat eye and ear infections, and pneumonia.

All children in developing countries diagnosed with measles should receive two doses of vitamin A supplements, given 24 hours apart. This treatment restores low vitamin A levels during measles that occur even in well-nourished children and can help prevent eye damage and blindness. Vitamin A supplements have been shown to reduce the number of deaths from measles by 50%.

Prevention

Routine measles vaccination for children combined with mass immunization campaigns in countries with high case and death rates are key public health strategies to reduce global measles deaths. The measles vaccine has been in use for over 40 years. It is safe, effective and inexpensive. It costs less than one US dollar to immunize a child against measles.

The measles vaccine is often incorporated with rubella and / or mumps vaccines in countries where these illnesses are problems. It is equally effective in the single or combined form.

In 2011, about 84% of the world's children received one dose of measles vaccine by their first birthday through routine health services – up from 72% in 2000. Two doses of the vaccine are recommended to ensure immunity and prevent outbreaks, as about 15% of vaccinated children fail to develop immunity from the first dose.

Overwhelming evidence demonstrates the benefit of providing universal access to measles and rubella-containing vaccines. Globally, an estimated 542,000 children died of measles in 2000. By 2011, the global push to improve vaccine coverage resulted in a 71% reduction in deaths. Since 2000, with support from the Measles & Rubella Initiative (M&R Initiative) over 1 billion children have been reached through mass vaccination campaigns – about 225 million of them in 2011.

In April 2012, the MR Initiative launched a new Global Measles and Rubella Strategic Plan which covers the period 2012-2020.

Implementation of the Strategic Plan can protect and improve the lives of children and their mothers throughout the world, rapidly and sustainably. The Plan provides clear strategies for country immunization managers, working with domestic and international partners, to achieve the 2015 and 2020 measles and rubella control and elimination goals. It builds on years of experience in implementing immunization programs and incorporates lessons from accelerated measles control and polio eradication initiatives.

2. PNEUMONIA

Introduction

Pneumonia is a form of acute respiratory infection that affects the lungs. The lungs are made up of small sacs called alveoli, which fill with air when a healthy person breathes. When an individual has pneumonia, the alveoli are filled with pus and fluid, which makes breathing painful and limits oxygen intake.

Pneumonia is the single largest cause of death in children worldwide. Every year, it kills an estimated 1.2 million children under the age of five years, accounting for 18% of all deaths of children under five years old worldwide. Pneumonia affects children and families everywhere, but is most prevalent in South Asia and sub-Saharan Africa. Children can be protected from pneumonia; it can be prevented with simple interventions, and treated with low-cost, low-tech medication and care.

KEY FACTS

- Pneumonia is the leading cause of death in children worldwide.
- Pneumonia kills an estimated 1.2 million children under the age of five years every year – more than AIDS, malaria and tuberculosis combined.
- Pneumonia can be caused by viruses, bacteria or fungi.
- Pneumonia can be prevented by immunization, adequate nutrition and by addressing environmental factors.
- Pneumonia caused by bacteria can be treated with antibiotics, but around 30% of children with pneumonia receive the antibiotics they need.

Causes

Pneumonia is caused by a number of infectious agents, including viruses, bacteria and fungi. The most common are:

- *Streptococcus pneumoniae* – the most common cause of bacterial pneumonia in children;
- *Haemophilus influenzae* type b (Hib) – the second most common cause of bacterial pneumonia;
- Respiratory syncytial virus is the most common viral cause of pneumonia;
- In infants infected with HIV, *Pneumocystis jiroveci* is one of the commonest causes of pneumonia, responsible for at least one quarter of all pneumonia deaths in HIV-infected infants.

Transmission

Pneumonia can be spread in a number of ways. The viruses and bacteria that are commonly found in a child's nose or throat can infect the lungs if they are inhaled. They may also spread via air-borne droplets from a cough or sneeze. In addition, pneumonia may spread through blood, especially during and shortly after birth. More research needs to be done on the different pathogens causing pneumonia and the ways they are transmitted, as this has critical importance for treatment and prevention.

Symptoms

The symptoms of viral and bacterial pneumonia are similar. However, the symptoms of viral pneumonia may be more numerous than the symptoms of bacterial pneumonia.

The symptoms of pneumonia include the following:

- rapid or difficult breathing
- cough
- fever
- chills
- loss of appetite
- wheezing (more common in viral infections)

When pneumonia becomes severe, children may experience lower chest wall in-drawing, where their chests move in or retract during inhalation (in a healthy person, the chest expands during inhalation). Very severely ill infants may be unable to feed or drink and may also experience unconsciousness, hypothermia and convulsions.

Risk factors

While most healthy children can fight the infection with their natural defenses, children whose immune systems are compromised are at higher risk of developing pneumonia. A child's immune system may be weakened by malnutrition or undernourishment, especially in infants who are not exclusively breastfed.

Pre-existing illnesses, such as symptomatic HIV infections and measles, also increase a child's risk of contracting pneumonia.

The following environmental factors also increase a child's susceptibility to pneumonia:

- indoor air pollution caused by cooking and heating with biomass fuels (such as wood or dung)
- living in crowded homes
- parental smoking

Treatment

Pneumonia caused by bacteria can be treated with antibiotics. These are usually prescribed at a health center or hospital, but the vast majority of cases of childhood pneumonia can be administered / managed effectively within the home with inexpensive oral antibiotics. Hospitalization is recommended in infants aged two months and younger, and also in very severe cases.

Prevention

Preventing pneumonia in children is an essential component of a strategy to reduce child mortality. Immunization against Hib, Pneumococcus, measles and whooping cough (pertussis) is the most effective way to prevent pneumonia.

Adequate nutrition is the key to improving children's natural defences, starting with exclusive breastfeeding for the first six months of life. In addition

to being effective in preventing pneumonia, it also helps to reduce the length of the illness, if a child does become ill. Addressing environmental factors such as indoor air pollution (by providing affordable clean indoor stoves, for example) and encouraging good hygiene in crowded homes also reduces the number of children who fall ill with pneumonia.

In children infected with HIV, the antibiotic cotrimoxazole is given daily to decrease the risk of contracting pneumonia.

3. HEPATITIS B

Introduction

Hepatitis B is a potentially life-threatening liver infection caused by the hepatitis B virus. It is a major global health problem and the most serious type of viral hepatitis. It can cause chronic liver disease and puts people at high risk of death from cirrhosis of the liver and liver cancer.

Worldwide, an estimated two billion people have been infected with the hepatitis B virus and more than 240 million have chronic (long-term) liver infections. About 600,000 people die every year due to the acute or chronic consequences of hepatitis B.

A vaccine against hepatitis B has been available since 1982. Hepatitis B vaccine is 95% effective in preventing infection and its chronic consequences, and is the first vaccine against a major human cancer.

The hepatitis B virus is not spread by contaminated food or water, and cannot be spread casually in the workplace. The incubation period of the hepatitis B virus is 90 days on average, but can vary from 30 to 180 days. The virus may be detected 30 to 60 days after infection and persists for variable periods of time.

KEY FACTS

- Hepatitis B is a viral infection that attacks the liver and can cause both acute and chronic disease.
- The virus is transmitted through contact with the blood or other body fluids of an infected person.
- Two billion people worldwide have been infected with the virus and about 600,000 people die every year due to the consequences of hepatitis B.
- The hepatitis B virus is 50 to 100 times more infectious than HIV.
- Hepatitis B is an important occupational hazard for health workers.
- Hepatitis B is preventable with the currently available safe and effective vaccine.

Geographical distribution

Hepatitis B virus can cause an acute illness with symptoms that last several weeks, including yellowing of the skin and eyes (jaundice), dark urine, extreme fatigue, nausea, vomiting and abdominal pain. Hepatitis B is endemic in China and other parts of Asia. Most people in this region become infected with the hepatitis B virus during childhood and 8 – 10% of the adult population is chronically infected. Liver cancer caused by hepatitis B is among the first three causes of death from cancer in men, and a major cause of cancer in women in this region.

High rates of chronic infections are also found in the Amazon and the southern parts of eastern and central Europe. In the Middle East and Indian subcontinent, an estimated 2 – 5% of the general population is chronically infected. Less than 1% of the population in Western Europe and North America is chronically infected.

Transmission

Hepatitis B virus is transmitted between people by direct blood-to-blood contact or semen and vaginal fluid of an infected person. Modes of transmission are the same as those for the human immunodeficiency virus (HIV), but the hepatitis B virus is 50 to 100 times more infectious. Unlike HIV, the hepatitis B virus can survive outside the body for at least seven days. During this time, the virus can still cause infection if it enters the body of a person who is not protected by the vaccine.

In developing countries, common modes of transmission are:

- perinatal (from mother to baby at birth)
- early childhood infections (inapparent infection through close interpersonal contact with infected household contacts)
- unsafe injection practices
- unsafe blood transfusions
- unprotected sexual contact

In many developed countries (e.g. those in Western Europe and North America), patterns of transmission are different from those in developing countries. The majority of infections in developed countries are transmitted during young adulthood by sexual activity and injecting drug use. Hepatitis B is a major infectious occupational hazard of health workers.

Symptoms

Most people do not experience any symptoms during the acute infection phase. However, some people have acute illness with symptoms that last several weeks, including yellowing of the skin and eyes (jaundice), dark urine, extreme fatigue, nausea, vomiting and abdominal pain.

In some people, the hepatitis B virus can also cause a chronic liver infection that can later develop into cirrhosis of the liver or liver cancer.

Who is at risk for chronic disease?

The likelihood that infection with the hepatitis B virus becomes chronic depends upon the age at which a person becomes infected. Young children who become infected with the hepatitis B virus are the most likely to develop chronic infections:

- 90% of infants infected during the first year of life develop chronic infections;
- 30 - 50% of children infected between one to four years of age develop chronic infections.

In adults

- 25% of adults who become chronically infected during childhood die from hepatitis B-related liver cancer or cirrhosis;
- 90% of healthy adults who are infected with the hepatitis B virus will recover and be completely rid of the virus within six months.

Diagnosis

A number of blood tests are available to diagnose and monitor people with hepatitis B. They can be used to distinguish acute and chronic infections.

Laboratory diagnosis of hepatitis B infection centers on the detection of the hepatitis B surface antigen HBsAg. A positive test for the hepatitis B surface antigen (HBsAg) indicates that the person has an active infection (either acute or chronic). WHO recommends that all blood donations are tested for this marker to avoid transmission to recipients.

Other commonly used tests include the following:

- Testing for antibodies to the hepatitis B surface antigen – a positive test indicates that the person has either recovered from an acute infection and cleared the virus, or has received a hepatitis B vaccine. The person is immune to future hepatitis B infection and is no longer contagious.
- Testing for antibodies to the hepatitis B core antigen – a positive test indicates that the person has had a recent infection or an infection in the past. Combined with a positive test for the hepatitis B surface antigen, a positive test usually indicates a chronic infection.

Treatment

There is no specific treatment for acute hepatitis B. Care is aimed at maintaining comfort and adequate nutritional balance, including replacement of fluids that are lost from vomiting and diarrhea.

Some people with chronic hepatitis B can be treated with drugs, including interferon and antiviral agents. Treatment can cost thousands of dollars per year and is not available to most people in developing countries.

Liver cancer is almost always fatal and often develops in people at an age when they are most productive and have family responsibilities. In developing countries, most people with liver cancer die within months of diagnosis. In high-income countries, surgery and chemotherapy can prolong life for up to a few years.

People with cirrhosis are sometimes given liver transplants, with varying success.

Prevention

The hepatitis B vaccine is the mainstay of hepatitis B prevention. WHO recommends that all infants receive the hepatitis B vaccine.

The vaccine can be given as either three or four separate doses, as part of existing routine immunization schedules. In areas where mother-to-infant spread of the hepatitis B virus is common, the first dose of vaccine should be given as soon as possible after birth (i.e., within 24 hours).

The complete vaccine series induces protective antibody levels in more than 95% of infants, children and young adults. Protection lasts at least 20 years and is possibly life-long.

All children and adolescents younger than 18 years old and not previously vaccinated should receive the vaccine. People in high risk groups should also be vaccinated, including:

- people with high-risk sexual behaviour
- partners and household contacts of infected people
- injecting drug users
- people who frequently require blood or blood products
- recipients of solid organ transplantation
- people at occupational risk of hepatitis B virus infection, including health-care workers
- travelers to countries with high rates of hepatitis B.

The vaccine has an outstanding record of safety and effectiveness. Since 1982, over one billion doses of hepatitis B vaccine have been used worldwide. In many countries, where 8 - 15% of children used to become chronically infected with the hepatitis B virus, vaccination has reduced the rate of chronic infection to less than 1% among immunized children.

As of July 2011, 179 countries vaccinate infants against hepatitis B as part of their vaccination schedules – a major increase compared with 31 countries in 1992, the year that the World Health Assembly passed a resolution to recommend global vaccination against hepatitis B.

4. OBESITY AND OVERWEIGHT

What are overweight and obesity?

Overweight and obesity are defined as abnormal or excessive fat accumulation that may impair health.

Body mass index (BMI) is a simple index of weight-for-height that is commonly used to classify overweight and obesity in adults. It is defined as a person's weight in kilograms divided by the square of his height in meters (kg / m2).

The WHO definition is:

- a BMI greater than or equal to 25 is overweight
- a BMI greater than or equal to 30 is obesity.

BMI provides the most useful population-level measure of overweight and obesity as it is the same for both sexes and for all ages of adults. However, it should be considered a rough guide because it may not correspond to the same degree of fatness in different individuals.

KEY FACTS

- Worldwide obesity has more than doubled since 1980.
- In 2008, more than 1.4 billion adults, 20 and older, were overweight. Of these over 200 million men and nearly 300 million women were obese.
- 65% of the world's population lives in countries where overweight and obesity kills more people than underweight.
- More than 40 million children under the age of five were overweight in 2010.
- Obesity is preventable.

Facts about overweight and obesity

Overweight and obesity are the fifth leading risk for global deaths. At least 2.8 million adults die each year as a result of being overweight or obese. In addition, 44% of the diabetes burden, 23% of the ischemic heart disease burden and between 7% and 41% of certain cancer burdens are attributable to overweight and obesity.

- Some WHO global estimates from 2008 follow.
- More than 1.4 billion adults, 20 and older, were overweight.
- Of these overweight adults, over 200 million men and nearly 300 million women were obese.
- Overall, more than one in ten of the world's adult population was obese.

In 2010, more than 40 million children under five were overweight. Once considered a high-income country problem, overweight and obesity are now on the rise in low- and middle-income countries, particularly in urban settings. Close to 35 million overweight children are living in developing countries and 8 million in developed countries.

Overweight and obesity are linked to more deaths worldwide than underweight. For example, 65% of the world's population live in countries where overweight and obesity kill more people than underweight (this includes all high-income and most middle-income countries).

What causes obesity and overweight?

The fundamental cause of obesity and overweight is an energy imbalance between calories consumed and calories expended. Globally, there has been:

- an increased intake of energy-dense foods that are high in fat, salt and sugars but low in vitamins, minerals and other micronutrients; and
- a decrease in physical activity due to the increasingly sedentary nature of many forms of work, changing modes of transportation, and increasing urbanization.
- Changes in dietary and physical activity patterns are often the result of environmental and societal changes associated with development and lack of supportive policies in sectors such as health, agriculture, transport, urban planning, environment, food processing, distribution, marketing and education.

What are common health consequences of overweight and obesity?

Raised BMI is a major risk factor for non-communicable diseases such as:

- cardiovascular diseases (mainly heart disease and stroke), which were the leading cause of death in 2008
- diabetes
- musculoskeletal disorders (especially osteoarthritis - a highly disabling degenerative disease of the joints)
- some cancers (endometrial, breast, and colon)

The risk for these noncommunicable diseases increases, with the increase in BMI. Childhood obesity is associated with a higher chance of obesity, premature death and disability in adulthood. But in addition to increased future risks, obese children experience breathing difficulties, increased risk of fractures, hypertension, early markers of cardiovascular disease, insulin resistance and psychological effects.

Facing a double burden of disease

Many low- and middle-income countries are now facing a "double burden" of disease.

- While they continue to deal with the problems of

infectious disease and under-nutrition, they are experiencing a rapid upsurge in non-communicable disease risk factors such as obesity and overweight, particularly in urban settings.
- It is not uncommon to find under-nutrition and obesity existing side-by-side within the same country, the same community and the same household.

Children in low- and middle-income countries are more vulnerable to inadequate pre-natal, infant and young child nutrition At the same time, they are exposed to high-fat, high-sugar, high-salt, energy-dense, micronutrient-poor foods, which tend to be lower in cost. These dietary patterns in conjunction with low levels of physical activity, result in sharp increases in childhood obesity while undernutrition issues remain unsolved.

How can overweight and obesity be reduced?

Overweight and obesity, as well as their related noncommunicable diseases, are largely preventable. Supportive environments and communities are fundamental in shaping people's choices, making the healthier choice of foods and regular physical activity the easiest choice, and therefore preventing obesity.

At the individual level, people can:
- limit energy intake from total fats;
- increase consumption of fruit and vegetables, as well as legumes, whole grains and nuts;
- limit the intake of sugars;
- engage in regular physical activity;
- achieve energy balance and a healthy weight.

Individual responsibility can only have its full effect where people have access to a healthy lifestyle. Therefore, at the societal level it is important to:
- support individuals in following the recommendations above, through sustained political commitment and the collaboration of many public and private stakeholders
- make regular physical activity and healthier dietary patterns affordable and easily accessible too all - especially the poorest individuals

The food industry can play a significant role in promoting healthy diets by:
- reducing the fat, sugar and salt content of processed foods
- ensuring that healthy and nutritious choices are available and affordable to all consumers
- practicing responsible marketing
- ensuring the availability of healthy food choices and supporting regular physical activity practice in the workplace.

5. SOIL-TRANSMITTED HELMINTH INFECTIONS

Overview

Soil-transmitted helminth infections are among the most common infections worldwide and affect the poorest and most deprived communities. They are caused by parasitic worms (helminths) that are transmitted to people through contaminated soil. The main species of soil-transmitted helminths that infect people are the roundworm (Ascaris lumbricoides), the whipworm (Trichuris trichiura) and the hookworms (Necator americanus and Ancylostoma duodenale).

KEY FACTS
- Soil-transmitted helminth infections are caused by different species of parasitic worms.
- They are transmitted by eggs present in human feces, which contaminate the soil in areas where sanitation is poor.
- Approximately two billion people are infected with soil-transmitted helminths worldwide.
- Infected children are physically, nutritionally and cognitively impaired.
- Control is based on:
- periodical de-worming to eliminate infecting worms
- health education to prevent reinfection
- improved sanitation to reduce soil contamination with infective eggs.
- Safe and effective medicines are available to control infection.

Global distribution and prevalence

More than 1.5 billion people or 24% of the world's population are infected with soil-transmitted helminth infections worldwide. Soil-transmitted helminth infections are widely distributed in tropical and subtropical areas, with the greatest numbers occurring in sub-Saharan Africa, the Americas, China and East Asia.

Over 270 million preschool-age children and over 600 million school-age children live in areas where these parasites are intensively transmitted, and are in need of treatment and preventive interventions.

Transmission

Soil-transmitted helminths are transmitted by eggs that are passed in the faeces of infected people. Adult worms live in the intestine where they produce thousands of eggs each day. In areas that lack adequate sanitation, these eggs contaminate the soil. People become infected with A. lumbricoides and T. trichiura by ingesting infective parasite eggs. This can happen in several ways.

- Eggs that are attached to vegetables are ingested when the vegetables are not carefully cooked, washed or peeled.
- Eggs are ingested from contaminated water sources.
- Eggs are ingested by children who play in soil and then put their hands in their mouths without washing them.

Hookworm eggs hatch in the soil, releasing larvae that mature into a form that can actively penetrate the skin. People become infected with hookworm primarily by walking barefoot on the contaminated soil.

There is no direct person-to-person transmission, or infection from fresh feces, because eggs passed in feces need about three weeks to mature in the soil before they become infective. Since these worms do not multiply in the human host, re-infection occurs only as a result of contact with infective stages in the environment.

Signs and symptoms

Morbidity is related to the number of worms harboured. People with light infections usually have no symptoms. Heavier infections can cause a range of symptoms including intestinal manifestations (Diarrhea, abdominal pain), general malaise and weakness, and impaired cognitive and physical development. Hookworms cause chronic intestinal blood loss that can result in anemia.

Nutritional effects

Soil-transmitted helminths impair the nutritional status of the people they infect in multiple ways.

- The worms feed on host tissues, including blood, which leads to a loss of iron and protein.
- The worms increase malabsorption of nutrients. In addition, roundworm may possibly compete for vitamin A in the intestine.
- Some soil-transmitted helminths also cause loss of appetite and therefore a reduction of nutritional intake and physical fitness. In particular, T. trichiura can cause Diarrhea and dysentery.

The nutritional impairment caused by soil-transmitted helminths is recognized to have a significant impact on growth and physical development.

WHO strategy for control

The strategy for control of soil-transmitted helminth infections is to control morbidity through the periodic treatment of at-risk people living in endemic areas. People at risk are:

- preschool children;
- school-age children;
- women of childbearing age (including pregnant women in the second and third trimesters and breastfeeding women); and
- adults in certain high-risk occupations, such as tea-pickers or miners.

WHO recommends periodic drug treatment (deworming) without previous individual diagnosis to all at-risk people living in endemic areas. Treatment should be given once a year when the prevalence of soil-transmitted helminth infections in the community is over 20%, and twice a year when the prevalence of soil-transmitted helminth infections in the community is over 50%. This intervention reduces morbidity by reducing the worm burden. In addition:

- health and hygiene education reduces transmission and reinfection by encouraging healthy behaviors;
- provision of adequate sanitation is also important but not always possible in resource-poor settings.

The aim of control activities is morbidity control: periodic treatment of at-risk populations will reduce the intensity of infection and protect infected individuals from morbidity.

Periodic de-worming can be easily integrated with child health days or supplementation programs for preschool children, or integrated with school health programs. In 2009, over 300 million preschool and school-age children were de-wormed in endemic countries, corresponding to 35% of the children at risk.

Schools provide a particularly good entry point for deworming activities, as they allow easy provision of the health and hygiene education component such as the promotion of hand washing and improved sanitation.

WHO-recommended medicines

The recommended medicines – albendazole (400 mg) and mebendazole (500 mg) – are effective, inexpensive and easy to administer by non-medical personnel (e.g. teachers). They have been through extensive safety testing and have been used in millions of people with few and minor side-effects. Both albendazole and mebendazole are donated to national ministries of health through WHO.

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