The hypo-hyper syndrome

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The coexistence of thyroid and parathyroid diseases is not rare. In the review of the recent literature, 25% of the patients with primary hyperparathyroidism (PHPT) had significant associated thyroid diseases including carcinoma in an Australian series.1 Regal et al2 reported a high prevalence of unsuspected varieties of thyroid disease occurring mainly in postmenopausal women in patients with PHPT in another series from Spain.2 Reciprocally, parathyroid pathology has been described in patients with primary thyroid disease. Sinaesi et al3 carried out the results of a recent Italian series of 221 thyroidectomies showed that 29 patients (13%) had a preoperative subclinical PHPT out of which 19 turned out to be due to parathyroid adenoma or hyperplasia.3 In this communication, we described a rare association of hypothyroidism as part of a polyglandular autoimmune syndrome (PAS) in a patient who in addition, found to have asymptomatic PHPT.

A 56-year-old Omani female and a mother of 10 children was attending the medical clinic for last few years for hypertension and hyperlipidemia. She was noticed to have developed several patches of vitiligo and had also complained of alopecia. She required a combination of atenolol, amlodipine, prazosin, indapamide, and losartan to control her hypertension. The patient had a hysterectomy in 1997, and a laparoscopic cholecystectomy in 2002. At a later point, she began to complain of bilateral pain and tingling in both hands, which turned out to be due to the carpal tunnel syndrome (CTS). Positive nerve conduction studies confirmed the diagnosis. That finding prompted further investigations for a possible underlying thyroid disease. Her serum free thyroxine (FT4) was low (6.07 pmol/l; normal = 9-19) with a high level of thyroid-stimulating hormone (TSH) (7.02 ulU/ml, normal = 0.35-4.94) and markedly elevated thyroid antibodies (antithyroglobulin levels of 546 U/ml, normal = 0-15 and anti-peroxidase antibodies levels of 350 U/l, normal = 0-32) were consistent with hypothyroidism due to autoimmune thyroid disease. Other investigations including the hemogram, blood chemistry, other endocrine workup, electrocardiogram, and relevant radiography were initially within normal limits or values. Serum B12 and folate were also within normal ranges. According to Betterle et al4 classification, the diagnosis of PAS type 3 on the basis of hypothyroidism secondary to autoimmune thyroiditis, vitiligo, and alopecia areata. There was no family history of similar illness. Antibodies for liver kidney microsomal, adrenal gland, gastric parietal cell, intrinsic factor, and acetylcholine receptor antibodies were negative. Facilities for tyrosinase and tyrosine hydroxylase antibodies were not available to our laboratory. The human leukocyte antigen typing revealed A2, A26, B8, B18, DR (17) 3, DR 52, and DQ 2. This haplotype is different from those commonly associated with type I PAS (A3 and A28) or type 2 (DR3/DQ81 or DR4/DQ81).3 We gradually commenced the L-thyroxine in increasing doses with noticeable improvement of the CTS symptoms on subsequent visits. We also achieved good suppression of TSH and normalization of serum thyroxine.

In further follow-up, we discovered that she has asymptomatic hypercalcemia due to PHPT following repeated routine assays of serum calcium and phosphorous. The calcium reached 12.7 and 12.9 mg/dl (normal = 8.5-10.5) along with marginally reduced level of phosphorous of 2.2 mg/dl (normal = 2.5-4 mg/dl) and repeatedly, markedly raised serum parathyroid hormone of 293 and 312 pg/ml (normal = 11-62 pg/ml). The urinary calcium excretion was 285 mg/day (normal = 100-300 mg/day). The radioisotope scan of the parathyroid glands (Tc 99m-sestamibi), and neck ultrasound examination both confirmed the presence of right inferior parathyroid adenoma. The clinical setting of hyperparathyroid adenoma in a hypertensive patient warranted further work-up to exclude multiple endocrine neoplasia (MEN) syndrome type I or type II A. Assays for serum prolactin, follicle stimulating hormone, luteinizing hormone, insulin, growth hormone, insulin-like growth factor, cortisol, adrenocorticotropic hormone, calcitonin, and 24 hours urine for vanillylmandelic acid (VMA) were within normal values. Serum gastrin was moderately elevated at 67 pmol (normal = 0-43); but not sufficiently high to diagnose pancreatic gastrinoma. Nonetheless, the Indium 111-Octreotide scan was negative for neuroendocrine tumor in pancreas or elsewhere in the abdominal cavity. The findings of the pituitary CT were negative for pituitary tumor and the iodine-131 metiodobenzylguanidine (MIBG) scans were negative for pheochromocytoma. Subsequently, she underwent successful excision of the parathyroid adenoma resulting in normalization of her serum calcium and phosphorous. The histopathology confirmed a well capsulated parathyroid adenoma with a wedge thyroid tissue showing focal lymphocytic thyroiditis. Polyclaglandular autoimmune syndrome 3 has been classified into 3 subcategories A, B and C. The latter is characterized by autoimmune thyroiditis with vitiligo and alopecia, or both and other organ.
specific disease excluding Addison’s disease. Obviously, the features of our patient were consistent with this subcategory. The PAS 3 is also known to be associated with other organ-specific and non-specific disorders such as sarcoidosis, celiac disease, myasthenia gravis, rheumatoid arthritis, and Sjogren’s syndrome. An associated gastric carcinoid syndrome was also reported. Autoimmunity, environmental, and genetic factors are the 3 major components of the pathophysiology of PAS. The presence of circulating organ-specific and cellular autoimmunity in patients with PAS 3 provides the strong evidence for the autoimmune pathogenesis of the disorder. Environmental precipitator/s such as viral infection, for example may exaggerate an ongoing immune response and precipitate glandular failure. In this regard, the links between congenital rubella infection and type 1 diabetes mellitus, and hypothyroidism is well known. Polyglandular autoimmune syndrome is often observed in subjects of the same family and suggested an autosomal dominant trait with variable penetrance. Certain genetic markers have been found to confer susceptibility to PAS 3, and the frequently described haplotypes include DR-*B*04/DQA1*0301/DQB1*0302, HLA-DR B1*13, DRB1*1104, and DRB1*0401. A significantly higher frequency of DR3 and DR4 antigens were also detected in patients with PAS 2 and 3 compared with controls in a recent study. Our patient exhibited A26, B8 and DR3 on tissue typing. It is of interest to note that the combination of A26 and B8 has recently been found to be an autoimmune favoring haplotype in Indians.

Evidently, this is an interesting combination of glandular hypo and hyper-function producing constellation of features of PAS type 3, and PHPT in the same patient. Although, the latter was the only apparent manifestation of the endocrine hyper-function, the patient was adequately investigated for a possibility of an associating or evolving MEN syndrome. However, a regular monitoring of the initially elevated serum gastrin would certainly remain imperative in the future management. Unfortunately, the patient lost to follow-up in the last 6 months, and relatives refused to be evaluated. Finally, the association of MEN and PAS is rarely reported in the English literature. We only managed to trace a single case report in which PAS was characterized by mucocutaneous candidiasis, vitiligo and macroglossia, and occurred together with Cushing’s disease and PHPT (MEN type 1).

References


Actinomyces meyeri isolation from synovial fluid of a patient with metastatic squamous cell lung carcinoma

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The genus actinomyces consists of several species of gram-positive, non-spore forming bacteria, which grow as obligate or facultative anaerobes. Actinomyces organisms are important constituents of the normal flora of mucous membranes. These organisms may produce infection after local trauma, surgery, or aspiration. The main forms of actinomycosis are cervicofacial, thoracic, and abdominal; most cases are due to Actinomyces israelii, whereas Garduno et al report occasional implication of other Actinomyces species. We rarely isolate Actinomyces meyeri (A. meyeri) in cases of actinomycosis. However, an increasing number of cases recognize its potential pathogenicity. In contrast to other species of Actinomyces, A. meyeri often causes pulmonary infection and shows a tendency for hematogenous dissemination. Involvement can include any organ of the human body so that a wide range of symptoms may be present. Although, multiple organs are involved, the outcome for these patients is excellent when we administer penicillin for several months and perform surgical procedures when necessary. As actinomycetes are rarely opportunistic agents in immunocompromised patients, the disease deserves special attention in those patients. Here, we report a case of actinomycosis with an uncommon localization that was due to A. meyeri in a patient with metastatic squamous cell lung carcinoma.
In April 2004, a 44-year-old woman complained of severe motion-dependent pain on her right hip. There were no signs of infection, and her complaints were considered to be due to lumbar disc herniation. In July 2004, she had to be hospitalized due to progressive pain by walking and proliferative plasma cell infiltration was detected from the biopsy of right caput femoris. A pathological fracture occurred after radiotherapy was applied to the femur. For this reason, Thompson prosthesis was applied. In November 2004, diffuse swelling on her left knee, on arcus mandibulae, and left frontal bone existed. Pathological examination of the biopsy from the left knee revealed metastatic squamous cell carcinoma, and she was transferred to the oncology service for chemotherapy planning and the investigation of the origin of the malignancy. The thoraco-abdominal CT scan revealed a soft tissue lesion of 65.36 mm size at the inferior lobe of left lung. On the posterior side of right sacroiliac joint, a metastatic soft tissue lesion of 70.42 mm size, causing destruction on the bone was detected. Furthermore, certain lytic and sclerotic lesions we observed on corpus vertebrae and posterior components of it. According to these findings, the diagnosis was determined as squamous cell lung carcinoma with metastatic bone lesions. She underwent a chemotherapy protocol consisting of cisplatin and etoposid. In addition, amoxicillin/sublactam we administered as empirical therapy. Meanwhile, synovial fluid obtained during biopsy was sent to our laboratory for microbiological examination. The obtained material was cultured aerobically and anaerobically; no microorganism were seen on gram stain. After 72 hours of incubation at 37°C, anaerobic blood agar plates (Brain heart infusion base supplemented with 5% sheep blood, 0.5% yeast extract, hemin, L-cysteine and vitamin K₃) yielded colonies of gram-positive, catalase negative bacilli in pure culture, subsequently identified as A. meyeri with use of the Rapid ID32 A system (bioMérieux, France). The isolated strain was found to be sensitive to all drugs tested by using ATB ANA system (bioMérieux, France). (Penicillin, amoxicillin, amoxicillin/klavulanic acid, piperacillin piperacillin/tazobactam, ticarcillin/klavulanic acid, cefoxitin, cefotetan, imipenem, clindamycin, chloramphenicol, metronidazole). After 10 days of chemotherapy, thrombocytopenia and neutropenia existed. In December 2004, her condition deteriorated and she died due to cardiopulmonary arrest.

The location of infections due to Actinomyces species is the cervico-facial region in 50-65% of the cases. The most frequently encountered germ is A. israelii, observed in 85% of the cases. Presenting clinical manifestations of actinomycotic infections are confusing as they often mimic other disease processes or even neoplasms. Diagnosis may be difficult due to this confusing clinical presentation combined with the fastidious nature of the organism in culture. We require a high index of suspicion to make an accurate and timely diagnosis and to institute the appropriate antibiotic therapy. Recently, emphasis is on the etiologic importance of anaerobic microorganisms in bone and joint infections in certain settings. These settings include recovery of Actinomyces species, hematogenously acquired infection, the presence of anaerobes in pure culture, and prosthetic-joint infection. Bussiere et al. reported 3 observations of osseous and articular actinomycosis. The associated soft tissue abscess with osseous lesions of the spine and limbs, and one of the patients had septic arthritis due to this bacterium: and obtained A. meyeri, from infectious foci in the 3 cases. The authors insisted on the rare occurrence, at that moment, of osteo-articular actinomycosis outside the maxillo-facial area. Here, we report an A. meyeri infection, which presented as arthritis. This case is of particular interest due to the extra pulmonary localization, and the rare species isolated. We could not isolate this bacterium from blood and sputum samples of the patient. In this case, we identified no underlying source of infection, so we suppose that an unrecognized disruption of the gastrointestinal mucosa could have been the portal of entry for A. meyeri, and then a hematogenous spread of the infection took place. The nature of the organism and its location to a joint are unusual features of this case. As the infection in the patient reported herein occurred only 4 months after hip surgery, we postulate a hematogenous spread from the patient’s own bacterial flora.

We did not receive any pathological data, and material for bacteriological culture from the lesions on os mandibulae and frontale existed at the same time with the lesion on the left knee, so we are not able to make a judgment that these lesions were certainly of malignant or bacteriological origin. But, we must emphasize the fact that actinomycosis can present in a variety of forms and may mimic other infections or even neoplasms. The diagnosis of severe actinomycosis parallel to neoplasia leads to speculation of a possible fortuitous association. To strengthen the hypothesis that we should suspect underlying conditions such as immuno-suppression in such disease, we report another case of actinomycosis associated with a malignant disease, namely, a squamous cell lung carcinoma. So this article stresses the importance of considering the diagnosis of the disease especially in immunsupressed patients with malignancies.
Actinomycye meyeri infection in malignancy

Utility of cefoxitin resistance determination by disk diffusion method for routine detection of meticillin resistant Staphylococcus aureus

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Methicillin resistant Staphylococcus aureus (MRSA) cause serious hospital acquired infections leading to high mortality, morbidity, and enhanced cost of patient management due to prolonged hospitalization. These strains are frequently resistant to multiple antibiotics, thus limiting the choice of antimicrobial therapy. Lately, there is an increasing trend of MRSA infections both in industrialized and developing countries. Prompt detection, identification, and confirmation of these strains by the clinical laboratories has a lot of infection control implications of rapid appropriate control measures to prevent its further spread in the hospital. Resistance to oxacillin by the disk diffusion method is the standard criteria of MRSA resistance. Recommendations to improve detection of MRSA include, incubation of disk diffusion test plates at lower temperature of 35°C for prolonged period, adding 2% sodium chloride (NaCl) to the susceptibility test medium and inoculation on Muller Hinton agar containing 4% NaCl with 6 µg/ml oxacillin. Available confirmatory tests for MRSA such as mecA gene analysis, latex agglutination test detecting PBP2a proteins are expensive and facilities for them are not available with all the clinical laboratories. Recently, the National Committee for Clinical Laboratory Standards (NCCLS) recommended cefoxitin disk diffusion test using standard susceptibility testing conditions for prediction of mecA mediated resistance in MRSA. The present study was carried out to compare the standard oxacillin salt agar confirmatory test to NCCLS cefoxitin disk diffusion test for detection of MRSA strains.

Methicillin resistant Staphylococcus aureus (MSSA) (n=436), and MRSA (n=109) were isolated from the clinical samples received from the patients admitted during January-December 2004, to the 500 bedded King Fahad Hospital and Tertiary Care Center, Al-Hofuf, Eastern region of Saudi Arabia. These strains were identified by Grams stain, catalase test, tube coagulase test, DNase test, and Staphaurex latex agglutination test (Murex Bio Tech, Dartford, UK). Methicillin resistant Staphylococcus aureus strains were identified on the basis of resistance to oxacillin 1 µg disk (Becton Dickinson Co, Maryland, USA) by standard disc diffusion method on Muller Hinton agar (Oxoid Ltd Basingstoke, Hampshire, UK) containing 2% NaCl. The plates were incubated at 35°C for 24 hours, and examined the zone of inhibition under the transmitted light for any colony or the growth film. The zone diameter less than 10 mm was considered as oxacillin resistance, and confirmed the oxacillin resistant strains as MRSA by inoculation on Muller Hinton agar with 4% NaCl, and 6 µg/ml oxacillin. Cefoxitin 30 µg (Becton Dickinson Co, Maryland, USA) disk diffusion confirmatory test was performed using standard test conditions on Muller Hinton agar and the plates incubated at 35°C for 24 hours. Zone of inhibition diameter less than 19 mm was considered as resistant and more than 20 mm as susceptible. The results of salt oxacillin agar confirmatory test for MRSA were compared with the NCCLS cefoxitin disk diffusion test. All the 436 MSSA were susceptible to cefoxitin (30 µg) with no discrepant results. Of the 108 strains of MRSA confirmed by inoculation on Muller Hinton agar containing 4% NaCl with 6 µg/ml oxacillin, all were resistant to cefoxitin (30 µg) by disk diffusion test. While one strain of MRSA, which had 9 mm zone of inhibition to one µg oxacillin disk but negative by salt agar

References

confirmatory test was also cefoxitin resistant (Table 1). Cefoxitin a cephemycin antibiotic is a very potent inducer of mecA expression; hence, resistant to it can be used as a predictor for the presence of mecA gene in MRSA strains. Previous studies, described high sensitivity and specificity of cefoxitin resistance with the disk diffusion method in confirmed MRSA strains. In the present study, cefoxitin resistance by disc diffusion method among MRSA strains had a sensitivity and specificity of 100%. Inclusion of cefoxitin (30 µg) disk in the routine sensitivity plates for *Staphylococcus aureus* appears to be a very simple, sensitive, specific, and cost effective method for confirmation of MRSA strains. The clinical laboratories, particularly in the developing regions of the world with over stretched health care budget, and limited recourses at their disposal, cannot afford the expensive molecular biological techniques for confirmation of MRSA. Testing of these strains routinely for cefoxitin resistance by disk diffusion test appears to be a better predictor of mecA mediated resistance in *Staphylococcus aureus*. This will not only be a cost effective, highly specific and sensitive test, but also the MRSA confirmation report can be made available to the clinicians in a much shorter time and can be very helpful in better management of the patient by timely prescribing the specific antimicrobial therapy, and implementation of strict infection control measures to control the spread of MRSA in the hospital.

Table 1 - Correlation of cefoxitin resistance among methicillin resistant and methicillin susceptible *Staphylococcus aureus*.

<table>
<thead>
<tr>
<th><em>Staphylococcus aureus</em> strains</th>
<th>Fox S/SOA Negative</th>
<th>Fox R/SOA Positive</th>
<th>Fox R/SOA Negative</th>
<th>Total</th>
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<tr>
<td>MSSA</td>
<td>436</td>
<td>Nil</td>
<td>Nil</td>
<td>436 (100)</td>
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<tr>
<td>MRSA</td>
<td>Nil</td>
<td>108</td>
<td>1</td>
<td>109 (100)</td>
</tr>
<tr>
<td>Total</td>
<td>436</td>
<td>108</td>
<td>1</td>
<td>545</td>
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</tbody>
</table>

MSSA - methicillin sensitive *Staphylococcus aureus*, MRSA - methicillin resistant *Staphylococcus aureus*, Fox - Cefoxitin, S - Susceptible, SOA - Sali Oxacillin agar, R - resistant

References


Role of maternal factors in the etiology of neural tube defects in Jordan

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Neural tube defects (NTDs) are among the most common human congenital malformations. Jordan lacks an ongoing surveillance system for congenital anomalies, however, the incidence of NTD in Jordan is high; 1.6 per 1,000 live births based on one study carried out in the north of Jordan. The exact cause of these defects is not known, however, they are currently considered to be “complex” genetic disorders with both genetic, and environmental factors play an important role in their causation. Nutritional factors appear to be an important contributor to the etiology of NTDs. Several other maternal factors have also been established to be contributory to this risk, including socioeconomic status, various environmental factors, genetic factors, maternal illness, and medication during pregnancy, maternal age and reproductive history. The risk of one child having spinal dysraphism is estimated at 0.1-0.2%, but with one affected sibling the risk of a second affected

Table 1 - Correlation of cefoxitin resistance among methicillin resistant and methicillin susceptible *Staphylococcus aureus*.
child increases to 2-5%, and the risk of a third affected child increases again to 10-15%. A small percentage of birth defects is preventable, hence, knowledge of any additive factor that increases the risk for a common birth defect, such as NTDs is relevant, and might help in planning preventive strategies. To identify whether risk factors associated with NTD in our population are similar to those in other populations or added factors play a role, this case control study was carried out at Jordan University Hospital using our patient population for the past 10 years. The charts of all patients hospitalized with NTD over a 10-year period between January 1993 and December 2002 were reviewed. A control group of 227 healthy live births born during the same period were also included for the chart review. It is noteworthy that for every patient 2 controls or more were chosen for the review. Controls were chosen from the same year as the patients. The charts were reviewed for maternal age, parity, birth order, previous abortions, previously malformed newborns, maternal illnesses, and drug history during pregnancy. The controls were reviewed in a similar way. Forty-five patients with NTD were included in the study. The average maternal age at birth in the study group was 27.34 years, while it was 28.45 years in the controls. There was no significant difference between the 2 groups (p=0.11). In addition, there was no significant difference in the 2 groups when further subdivided by age. Spontaneous abortions were reported in 47.5% of NTD mothers compared with 27.9% of the controls, and the difference between the 2 groups was significant (p<0.05). Regarding parity, 31.7% of mothers of NTD children were primiparous compared with 20.4% in the controls. While there was no significant difference, a trend towards correlation with primipara was noted, 31.7% versus 20.4%. In addition, neither birth order, nor maternal illness nor drug history was significant in this study.

The NTD rates vary from one population to another, and have also been found to vary by geography, time, maternal demographic characteristics, and maternal reproductive history. The effect of maternal age as a risk factor for NTDs is generally considered to be small, and when an association can be found, risk tends to be elevated in older or very young mothers. In our group of patients, we failed to elicit such a role for maternal age. A history of spontaneous abortion was reported in 47.5% of NTD mothers compared with 27.9% in the controls, and this showed a significant relation (p=0.01). An association between NTDs, and previous spontaneous abortions has been noted in several studies, and there are several suggested hypotheses for the explanation of this observation; Firstly, the trophoblastic cell rest theory, the remaining from a previous aborted pregnancy interferes with normal embryogenesis and secondly, previously lost fetus was affected with NTD, however, genetic factors might also be incrimented as well. Some birth defects can be associated with higher birth order, but in this study, there was no correlation between birth ordered and risk of NTD. Some authors reported a correlation between multiparity and NTD others have shown both a "modest risk in mothers of parity 3 or more" and an increased risk in primiparous mothers. While there was no significant difference in our study, a trend towards correlation with primipara was noted. Maternal illness during pregnancy has also been considered a risk factor. Pregestational diabetes increases the risk of having a child with a malformation in the central nervous system including spina bifida to 2-10 fold higher than the risk in the general population, in addition a febrile illness in the first trimester has been associated with a 2-fold increase in the risk. In utero exposure to drugs such as valproic acid, and carbamazepine increase the risk of spina bifida to 1-2%. In this study neither maternal illness nor drug history was significant. Controlled interventional studies have clearly shown a 72% reduction in the risk of NTDs with the use of folic acid dietary supplements, and based on the results of this study periconceptional supplementation with folic acid might be useful in reducing the risk of NTD in mothers with high risk history.

Acknowledgment. This study was supported by a grant from the University of Jordan. The author is grateful to Dr. Abd Allatif Thabet for his help in data collection.

Received 25th June 2005. Accepted for publication in final form 10th September 2005.

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