Paget’s disease of the bone. A decade since the first reported case.

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ABSTRACT
Paget’s disease of the bone is a disease which is frequently encountered in populations of European origin. It is very rare in the Middle East and in the Arabian Peninsula. Only very few cases have been reported in the literature. Nevertheless, it is a fascinating disease in its etiology, pathogenesis and modes of presentation. Over the last two decades or more many advances have been made in diagnostic and treatment modalities of the disease. Here we report another rare case of paget’s disease in a Saudi female, with the objective of shedding light on this rare entity in Saudi Arabia. We review the new advances made in delineating the pathogenesis of it as well as the new techniques in diagnosis and state of the art medical treatment available. Hoping that this will attract the attention of specialists interested in this disease and that more cases if encountered are to be reported.

Keywords: Paget’s disease, bones, pathogenesis treatment.

Paget’s disease of the bone is a relatively common disorder in populations of mainly European origin. The incidence has been estimated to be around 3-4% of adults over the age of 40, based on autopsy results. It is rare in the Middle East and Far Eastern Countries. N. J. Y. Woodhouse et al described the first Saudi patient in the literature in 1988 and in the same year, a reply to the editor, stated that he saw five cases in the preceding 9 years which were misdiagnosed, but he did not state their nationalities. The rarity of this disorder in the Middle East is presumably due to a difference in the genetic make up of the population and the geographical and climatic influence of the environment on the disease. Paget’s disease is common in caucasion of tempreament climates who might be more susceptible to certain viral infections that could trigger the pathological process of the disease. Advances in the investigational tools and treatment modalities have been made since the early reports and here we describe another case of Paget’s disease in a Saudi female and the progress of her disease.

Case Report. A 58 year old Saudi female presented in 1994 with history of low back pain for around two years and joints pain mainly of the left hip causing some problems with mobilization and was was painful for her to rise from a sitting position. She sustained a DVT post delivery in the right leg 9 years ago. There was nothing remarkable on examination except for being overweight and no bony deformities were detected.

Investigations. Showed bone profile Ca 2.3 mmol/L (2.1 - 2.6) PO4 1.2 mmol/L (0.8 - 1.4) Alp 428 U/L (43 - 154). An old profile done 10 years previously showed high Alp of 330 U/L. Radiological investigations including X-ray pelvis and femure (Fig 1a, 1b) and a bone scan (Fig 2) showed typical presentation with affection of right ilium and left femoral head and neck in a disordered bony formation which was hot on bone scan.

Patient was prescribed intranasal calcitonin with Vit D and calcium and showed mild improvement in pain and mobility after 3 months of therapy. Unfortunately she could not continue this medication as it was not available for sometime. Her pain increased and Alp activity increased to 778 so decision was made to admit her for IV clodronate therapy (Cl3MDP). She received 300 mg of clodronate in 300 cc of normal saline over 3 hours, repeated for five days with measurement of electrolytes, liver function test, bone profile, urinary hydroxyproline and deoxypyridinoline crosslinks before and throughout the period of treatment.

Her electrolytes and LFT remained in the normal.
range. Unfortunately the urinary deoxypyridinoline crosslinks samples were not all assessed and we ended with only two, a baseline of 200 nm/m creatinine and a reading during or after treatment of 120 nm (normal range 2-6 nm/m creatinine) which proved that the level of collagen breakdown metabolites to dropped. Hydroxyproline could not be assessed in our laboratory.

**Discussion.** Osteitis deformans or Paget’s disease of the bone (paget 1877) is a metabolic disorder of bone which is not hormone-dependent. It is very common in parts of Europe and the USA and is extremely uncommon in the Arabian Peninsula. Pathologically the disease starts as a focal benign disorder which might be monoosostotic or polyostotic with expansion of bones secondary to diffuse abnormal remodelling and abnormal positive tissue balance leading to hypertrophy and osteosclerosis with expansion of affected bones, and it is considered to be a cardinal sign in paget’s disease Jaffe 1933, Milgram 1977. Histologically the affected bones show increased fibrovascular tissue and abnormal osteous structure Jaffe 1933.

The basic anomaly is a disturbed bone multicellular units (BMUS) activity with abnormal excessive resorption by osteoclasts followed by disordered bone formation with disorganized lamellar texture leading to both qualitative and quantitative dysfunction of bone with increased risk of fractures. The majority of patients are asymptomatic. Those with symptoms commonly present with musculo skeletal complaints including osseous deformities, fractures, neoplasms, soft tissue masses, osteomyelitis, extramedullary hematopoiesis, joints crystal deposition, neurological abnormalities and degenerative joint disease.

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Figure 1a,1b - X-ray pelvis, femur and hips showing increased bone density with exaggeration of trabeculation in right ilium and left femoral head and neck as well as proximal third of femur with bone expansion noted in the diaphysis of femoral shaft with sclerosis of symphysis pubis.

Figure 2 - Total body bone scan with marked increased activity in pelvis, and left femur corresponding to the same affected areas on plain x-ray.
Although the cause of the disease is still not entirely clear, all of the experimental evidence seem to support the theory of a persistent slow developing viral infection of the osteoclasts probably a paramyxovirus. This is based on the presence of viral like inclusions of the paramyxoviral family found in the osteoclasts of pagetic bones Mills et al 1984,11 and Lai et al 1989.12 Both RSV and/or MV antigens have been detected in active lesions of pagetic bones Mills et al 1984(11), Basle et al,13 Mills et al 1986,14 and Reddy et al 1992.15 Nevertheless a virus has not been yet isolated from the abnormal osteoclasts, and it is yet to be confirmed whether the presence of the viral like antigens are disease specific or a secondary phenomenon.1

The disease has a predilection for the axial skeleton, and proximal long bones particularly the femur, a preference for the lower extremities and a tendency for right sided lesions10 which was observed in our case.

The initial destructive phase of the pagetic process is generally not appreciated on X-rays except when it involves the skull or long bones.1 Radiological evidence of the disease becomes apparent in the subsequent phases with dense areas of focally disrupted architecture and expanded bones, widened cortex and coarse trabeculation. The disease may remain sharply localized and have little clinical significant and this is common in many patients.2 Symptoms and signs usually appear when the disease is multifocal or intensively active metabolically.2,3 Scintigraphy is more sensitive than radiography in detection of Paget's disease.16 It shows a distinct increase in radionucleotide accumulation in the affected area and it is valuable in assessing the extent of the disease.17,18 It is a good marker of therapeutic response19 and it can also pick recurrence of the disease before biochemical markers.10

The marked increase in bone remodeling allows for the utilization of bone turnover markers in the assessment of activity of the disease and response to treatment. The urinary excretion of pyridinoline cross-links is at present the most promising marker of bone resorption.20 Pyridinoline (Pyr) and deoxypyridinoline (D-Pyr) are released from bone matrix during its degradation by the osteoclasts. They are reported to be more sensitive than Hydroxyproline, are relatively specific for bone turnover, and do not appear to be metabolized in vivo before their urinary excretion.21 They are being used with increasing frequency in all forms of metabolic bone diseases and they have yielded great help in the assessment of treatment. In Paget's disease it has been reported to reduce by 71% after only 3 days of I.V. bisphosphonate therapy.21 Its clinical use was limited in the past by the need for HPLC which is cumbersome and a tedious technique as well as being time consuming. A new ELISA based technique was developed in 199022 which has made the use of such a test relatively simpler and more convenient and has made such a tool invaluable in assessing the disease and following up the progress of its treatment.

Effective therapeutic modalities have been available only since 1950 and disease modifying treatment has been available in the late 1960's. Among them is calcitonin which act as a potent inhibitor of bone resorption and can also relieve pain. It reduces the levels of Alkaline Phosphatase (ALP) and hydroxyprolin, and improvement in radiological appearance has been reported especially during the osteolytic phase of the disease.14 Certain problems exist with calcitonin therapy, the plateau phenomenon (high serum alkaline phosphatase cannot be lowered further whatever dose given) which is seen in most patients after few months of therapy, resistance to the treatment with formation of antibodies to the drug, and a rebound response is seen in some patients despite continued therapy.23,24 Mithramycin is an antibiotic with cytotoxic activity and has been used in treatment of paget's disease with reduction in bone pain and improvement in laboratory parameters of disease activity25 as well as improvement in radiographic and scintigraphic appearance.26 But since it is a toxic drug it is reserved for the difficult resistant cases which do not respond to the standard treatment.

The Bisphosphonates are the other agents which inhibit bone resorption by binding to the hydroxyapatite crystals and inhibiting their growth and dissolution.27 It decreases skeletal pain with reduction of Alp activity and hydroxyproline levels28,29 and in some cases conversion of pagetic bone to normal tissue. EHDP (etidronate) was the first of this group studied in 1971 by Smith et al.28 However, many of the original studies indicate that prolonged high doses produce osteomalacia. APD (pamidronate) is the most potent of this group in current use with dramatic radiological and biochemical healing as well as prolonged remission period.23 Over the last 20 years there is an increasing evidence in literature to support that bisphosphonate especially APD lead to dramatic healing of bone with marked reduction in bone turn over, reduction in active bone resoring surface with restoration of orderly lamellar bone which is laid down30 after treatment. The long term response to a short course of intravenous bisphosphonate is very good and may emerge as a standard treatment in the future. Newer bisphosphonates are also reported to be safe and effective and the indications for therapy may widen to include prophylactic treatment for the young asymptomatic patients.23 Combining calcitonin and bisphosphonate has been shown by some to give better remission rate.30,31

In our patient the response to the I.V. cloonanate therapy was significant where pain was concerned and the limited samples of collagen breakdown
metabolites showed significant response to therapy with no notable side effects clinically or biochemically from this therapy.

In summary the future looks brighter for patients with Paget's disease as the new bisphosphonates prove their efficacy, safety and the cost is more affordable. The disease is rare in the Middle East and Arabian Peninsula but one should be aware of it as effective modalities of treatment are available.

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References