A tale of three diseases of the bone

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ABSTRACT

Paget's disease is a relatively rare disorder of the bone with only a few reports and case series observations from India. Hypocalcaemia is rare in Paget's disease, usually occurring as a consequence of therapy with bisphosphonates. We report a 65-year-old woman with Paget's disease who had hypocalcaemia secondary to vitamin D deficiency. On further evaluation, she also had severe osteoporosis. How vitamin D deficiency affects the diagnosis and monitoring of Paget's disease and the relationship between the three diseases are discussed. This case illustrates an interesting situation with abnormal bone turnover, remodelling and mineralisation in the form of Paget's disease with osteomalacia and osteoporosis.

Keywords: hypocalcaemia, osteomalacia, osteoporosis, Paget's disease, vitamin D deficiency

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INTRODUCTION

Paget's disease is a focal disorder of accelerated skeletal remodelling that can involve either a single bone (mono-ostotic) or multiple bones (polyostotic). There is excessive bone resorption, followed by excessive bone formation, leading to a highly vascularised bone that is structurally disorganised. This results in bone pain, deformity, skeletal fragility and pathological fractures.[1] Paramyxoviruses and genetic susceptibility are postulated to play a role in the aetiology.[1] The prevalence of Paget's disease in the western countries is about 1%–2% and is reported to be rare in the Asian countries.[1] Only a few case series from India have been recently reported.[2,3] The role of vitamin D metabolism in Paget's disease is not clear. The correlation between vitamin D metabolites and markers of bone remodelling has been a subject of intense research. However, the prevalence and association of vitamin D deficiency in Paget's disease has not been studied in detail. We report a case of Paget's disease with vitamin D deficiency and osteoporosis, and discuss how these disorders relate to each other in the diagnosis and management.

CASE REPORT

A 65-year-old woman was seen at the emergency department for complaints of pain in the right hip and inability to walk. She was on treatment for diabetes mellitus, hypertension, dyslipidaemia and ischaemic heart disease. On examination, her right hip was externally rotated with restriction of all movements. Radiograph of the pelvis done at the emergency department showed a mixed sclerotic lesion involving the right ilium, ischium and pubic rami. Cortex of the right femoral head was distorted and the hip joint appeared elevated. The left side of the pelvis and the left hip joint appeared normal. A radiological diagnosis of Paget's disease of the right hemipelvis was made. A detailed history revealed that the patient attained early menopause at the age of 40 years. Her dietary intake of calcium was approximately 800 mg and vitamin D less than 200 IU per day. Sun exposure was inadequate. She was not on calcium and vitamin D supplements. There was no family history of bone disease. Her blood investigations showed a low calcium (1.9 [normal range 2.2–2.6] mmol/L), low phosphorus (0.8 [normal 1.0–1.4] mmol/L) and a raised alkaline phosphatase (466 [normal < 200] IU/ml) level. Her liver functions and renal functions were normal. Her 25-hydroxyvitamin D3 was low at 14 (normal 37.4–200) nmol/L.

A whole body Tc-99m methylene diphosphonate (MDP) bone scan revealed an increased uptake in the right hemipelvis, and fifth and sixth ribs on both sides. A diagnosis of Paget's disease of the right hemipelvis with Vitamin D deficiency was made. She was treated with intramuscular cholecalciferol (six lakh units intramuscularly) and oral calcium carbonate (1,250 mg twice daily) and elemental calcium 500 mg twice daily). On review after two months, the patient was symptomatically better and her serum alkaline phosphatase (SAP) was 367 IU/ml, calcium 2.3 mmol/L and phosphorus 1.1 mmol/L. She was then given 4 mg of zoledronic acid intravenously for her Paget's disease and was asked to continue calcium supplements. After four weeks, her SAP dropped down to 153 IU/ml. In view of her early menopause, a bone mineral density (BMD) was estimated using a dual energy X-ray absorptiometry (DEXA) scan of her left hip and lumbar spine. The T-score of the hip was –3.3, Z-score –1.6, with a total area of 0.686 g/cm^2. The T-score of the lumbar spine (L1–L4) was –3.3, Z-score was –1.4, with an area of 0.487 g/cm^2. As she was already on anti-resorptive agents for the Paget's disease, she was advised to continue calcium supplements, monitor SAP every two months and undergo BMD testing every two years. A repeat dose of zoledronic acid is contemplated, depending on the SAP levels on follow-up.

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DISCUSSION

The usual investigations done in a patient with Paget's disease include a calcium profile, SAP and a radionuclide bone scan. Calcium levels are usually normal in Paget's disease. Hypercalcaemia is seen with immobilisation associated hyperparathyroidism. Hypocalcaemia can occur during therapy with bisphosphonates. However, the presence of hypocalcaemia at the time of diagnosis, as in our patient, should alert one to the possibility of a coexisting vitamin D deficiency. The measurement of SAP provides a clinically useful index of osteoblastic activity in the absence of significant liver disease or pregnancy.[1] SAP levels correlate with both the extent and activity of the Paget's disease.[4] Levels of SAP are used to monitor therapy, but the response is slow and a definitive result is seen after 4–8 weeks, when compared with the markers of osteoclastic activity. Radionuclide bone scan is done in Paget's disease primarily to know the extent of skeletal involvement.[5]

The prevalence of vitamin D deficiency among pagetic patients is not known. From a series of 17 cases reported from western India, only two patients had 25-hydroxyvitamin D levels below 10 nmol/L.[3] The aetiology of vitamin D deficiency in Paget's disease may be more than simply nutritional. During the phase of increased osteoblastic activity, there may be an increased need for vitamin D for mineralisation of the newly-formed osteoid. This increased demand can precipitate a frank vitamin D deficiency in those with borderline stores, leading to osteomalacia of their non-pagetic skeleton. Even patients with normal stores of vitamin D may fail to meet the increased demands of Paget's disease.

This concept of relative vitamin D deficiency was initially suggested by Williams et al in their observation of 14 patients with biopsy-proven Paget's patients.[6] They found that areas of bone with a high turnover showed localised osteomalacia when the vitamin D levels were in the lower limits of the normal range. In a study by Devlin et al,[7] the levels of serum 25-hydroxyvitamin D3 and 24,25-dihydroxyvitamin D3 in pagetic patients (36 patients) were significantly lower than in age-matched controls. In another study by Foldes et al in 23 patients with Paget's disease, values of 25-hydroxyvitamin D3 and 24,25-dihydroxyvitamin D3 were within the normal range in most (more than 90%) of the subjects.[8] 1,25-dihydroxyvitamin D3 was increased in 11 (48%) patients in whom the mean serum alkaline phosphatase activity was insignificantly higher. We hypothesise that the elevated level of 1,25-dihydroxyvitamin D3 may be due to a relative Vitamin D deficiency, which results in increased parathyroid hormone (PTH) levels. Increased PTH stimulates 1-alpha hydroxylase activity in the kidney, leading to a relative increase in 1,25-dihydroxyvitamin D3 and a relative fall in the levels of 25-hydroxyvitamin D3 and 24,25-dihydroxyvitamin D3. Current studies also suggest a role for the vitamin D metabolites in the activity of Paget's disease and hypersensitivity of vitamin D receptor among the pagetic osteoclast precursors.[9-11]

Vitamin D deficiency can result in an elevation of SAP, thus confounding diagnosis and monitoring of Paget's disease. It can result in poor mineralisation of the newly-formed osteoid, further weakening an already weak bone. Radionuclide bone scan cannot distinguish between Paget's disease, Looser's zone and microfractures, thus making it difficult to assess the actual extent of Paget's disease. Bisphosphonates are currently the agents of choice for treatment of Paget's disease. Bisphosphonate-induced osteomalacia has been previously reported with etidronate.[12] Newer bisphosphonates used parenterally for malignancies has precipitated hypocalcaemia in patients who were Vitamin D deficient.[13] Hence, it is imperative to screen and correct vitamin D deficiency in every patient with Paget's disease. Osteoporosis may occur locally during the resorptive phase of Paget's. Fortunately, osteoporosis does not raise a management issue in Paget's disease, as bisphosphonates can be used for both the diseases. It has been well-recognised that there is a high prevalence of vitamin D deficiency among elderly osteoporotic women, and correction of calcium and vitamin D reduces fracture incidence.[14,15] Considering the effects of bisphosphonates on vitamin D, it is advisable to screen all patients with osteoporosis for vitamin D deficiency before initiating anti-resorptive therapy.

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