



Paget's Disease of Bone : Experience from a Centre in Southern India

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Abstract

Background : Paget's disease is a localized disorder of the skeleton characterized by increased osteoclastic activity. While the prevalence in the Western Population is 1-2%, the prevalence in India is not known. We studied the clinical profile, biochemical parameters, bone scans, therapeutic details and follow up data of patients with Paget's disease, attending the Endocrinology outpatient clinic in our institution.

Methods : A retrospective review was done of the medical records of 51 patients seen in a tertiary referral centre in Southern India from 1995 to 2003. The data was analyzed using SPSS 9.0 software package.

Results : There were a total of 51 patients (41 male and 10 female). The mean age at presentation was 56 years and the mean duration of symptoms was 43 months. At least 6 months of follow-up was available in 31 patients and longer term (>2 years) follow-up in 22 patients. The symptoms at presentation were bone pain in 65%, low backache in 37%, skeletal deformities in 33%, pathological fractures in 20%, neurogenic claudication in 4%, deafness and head enlargement in 7% and renal stones in 4% of subjects. Five patients (9.8%) were asymptomatic and were incidentally diagnosed during evaluation of an elevated alkaline phosphatase. The mean serum alkaline phosphatase (range and SD) at the time of presentation was 690 IU/L (91-3873 U/L, 698 U/L). There was no statistically significant difference in the serum alkaline phosphatase values between female and male patients (576 U/L versus 718 U/L). Polyostotic involvement was seen in 90.2% of the patients. The pattern of skeletal involvement was very similar to that described in the Western literature. Twenty patients were started on Calcitonin and of these, 13 patients were later changed over to bisphosphonates to induce remission. In all, thirty six subjects received Alendronate and of them, 31 received lower doses (10-20mg/day). All the treated patients showed a good clinical and biochemical improvement. Two patients with severe Pagetic involvement of the bone who also had neurologic symptoms (root pains in one and cauda equina lesion in the other) needed intravenous Pamidronate to obtain a rapid response in the initial phase of treatment.

Conclusions : In our series, Paget's disease had a male predominance. The clinical presentation and the pattern of skeletal involvement was similar to the Western series. Serum alkaline phosphatase declined by 40% at 6 months of therapy and by 64% by one year of treatment in patients who were on lower doses of Alendronate (10-20 mg/day) in our series, which is similar to what has been described with conventional doses (40 mg per day) in the Western series. ©

INTRODUCTION

Paget's disease of bone, which was first described by Sir James Paget in 1877, is a focal disorder of accelerated skeletal remodeling that can involve a single or multiple bones. It is characterized by excessive bone resorption followed by excessive bone formation, resulting in an abnormal highly vascularized bone that is structurally disorganized, with an excess of fibrous connective tissue.³ While this process may remain

clinically silent in the early stages, the majority of patients present with bone pain, skeletal deformity and pathological fractures. Rarely, there is neurologic involvement. While a viral aetiology has been proposed, a genetic component probably plays an additional role.⁶ The estimates of prevalence in the Western population have been 1-2%.^{7,9} and the disease is believed to be rare in Asians. However no prospective studies are available in Asian subjects. With the wider availability of radionuclide bone scans, routine biochemical screening and radiology, more patients are being diagnosed early in the course of the disease. In India, the prevalence of Paget's disease is unknown and there is very limited published literature.^{4,5} Hence, we conducted a

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retrospective study of our patients with Paget's disease who visited the referral Endocrinology clinic in a tertiary care institution.

PATIENTS AND METHODS

We retrospectively analysed the data obtained from the medical records of 51 patients with Paget's disease, registered in our hospital from 1995 to 2003. Clinical data such as age at presentation, symptoms, duration and presence of complications were analyzed. The family history was studied to look for a familial occurrence. Blood biochemistry included serum total alkaline phosphatase (at presentation and at subsequent visits), fasting serum calcium, phosphate, uric acid, urinary calcium and phosphate parameters. Skeletal involvement was studied using radiography and bone scans, which were repeated later to assess the clinical response to treatment.

Therapeutic details included the medications used, the clinical response as seen by symptom relief, reduction in the levels of serum alkaline phosphatase, and degree of skeletal involvement as shown by the bone scans. Sixteen patients who had registered in the initial part of the study had also undergone histologic evaluation of bone biopsy specimens (Fig. 1).

RESULTS

Demographic characteristics

Data from the medical records of 51 patients was analysed. There were 41(80%) males and 10(20%) females (M:F::4.1:1). The mean age (range) at presentation was 56 years (12 -76). The age distribution is presented in Fig. 2. Most of the patients were from Tamil Nadu (73%) while a small number were from West Bengal (8%) and Madhya Pradesh (8%) with the occasional subjects from other parts of India and 1 patient from Bhutan. This pattern is probably reflective of the referral pattern to our institution. In our series, there were 2 brothers from one family with Paget's disease.

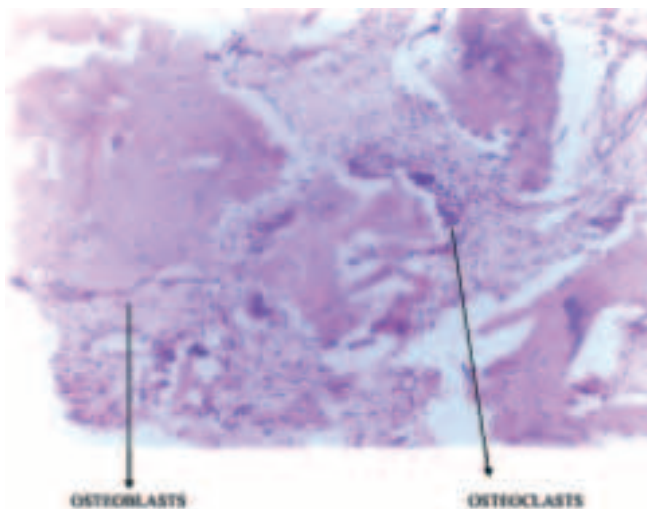


Fig. 1 : Histopathology of a bone biopsy specimen.

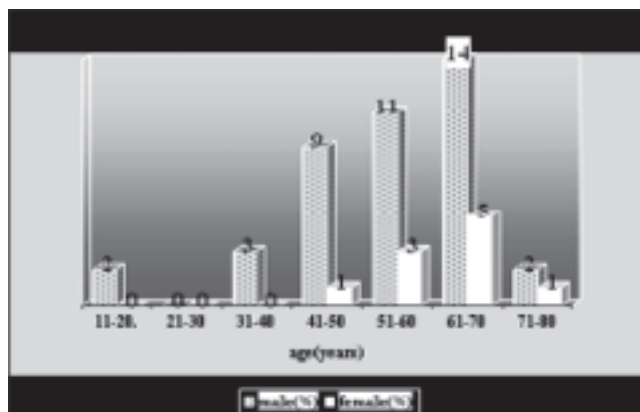


Fig. 2 : Age and sex distribution of the patients.

Symptoms at presentation

The mean duration of symptoms was 43 months (1-120). Five subjects (9.8%) were asymptomatic and had been referred to our department as they had elevated serum alkaline phosphatase. Of those who were symptomatic, the common presenting symptoms were as follows:- bone pain (65.2%), low backache (36.9%), skeletal deformities (32.6%), pathological fractures (19.6%), deafness (6.5%), skull enlargement (6.5%), neurogenic claudication (4.3%), renal stones (4.3%) and painless swelling (2.2%).

Skeletal involvement

Monoostotic Paget's disease was seen in 5/51(9.8%) subjects, the remaining 46/51(90.2%) had polyostotic involvement of the bone. A representative bone scan from a patient with polyostotic Paget's disease is shown in Fig. 3.

On radiologic evaluation and on bone scans, the skeletal sites involved were as follows:

Pelvis - 64.6%	Sternum - 14.6%
Spine - 54.2%	Scapula - 10.4%
Femur - 45.8%	Clavicle - 10.4%
Skull - 45.8%	Sacrum - 8.3%
Tibia - 43.8%	Radius - 6.2%
Humerus - 29.2%	Talus - 4.2%
Ribs - 27.1%	Calcaneum - 4.2%

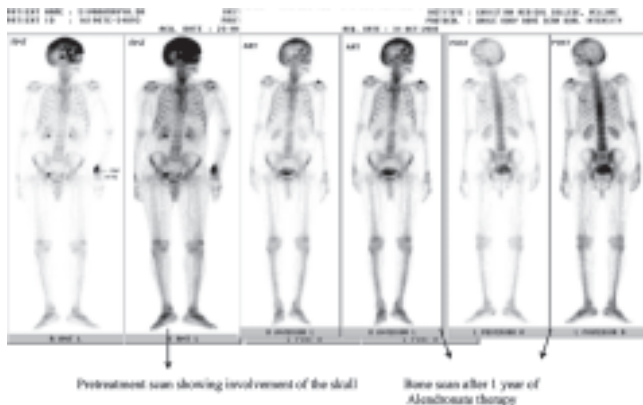


Fig. 3 : Pretreatment and posttreatment bone scans.

Uncommon sites included –foot bones, phalanx, ulna and fibula (2% each).

Disease complications

Of the various disease complications, hyperuricemia (17.6%) and deafness(11.8%) were relatively common. Of the 9 patients with hyperuricemia, 2 had gout and 2 had renal stones. Secondary osteoarthritis (5.8%), radiculopathy (5.8%), renal stones (3.9%) and symptomatic gout (3.9%) were less commonly encountered. There were 12 patients with associated systemic hypertension, three with documented coronary heart disease, one with rheumatic heart disease and one with aortic dissection in the past. None of the patients had high output cardiac failure or osteosarcoma of the bones. Two patients had unrelated malignancies (one had carcinoma larynx and the other had multiple myeloma).

Biochemical parameters

The mean serum alkaline phosphatase at the time of diagnosis was 690 U/L (91 –3873 U/L, SD – 698 U/L). There was no statistically significant difference in mean serum alkaline phosphatase values between affected women and men (576 U/L in women and 718 U/L in men). Nine (17.6%) subjects had hyperuricemia, of whom two had renal stones and two had gout. Serum calcium and phosphate were normal except in one patient with multiple myeloma who had hypercalcemia (serum calcium –18 mg%). None of the patients had coexistent hyperparathyroidism.

Treatment

During the initial 4 years of the study, only Salmon Calcitonin and Etidronate were available in India. Twenty (39.2%) patients were started on calcitonin injections and 5 patients on etidronate. These 18 patients were later placed on oral or parenteral bisphosphonates to induce remission.

Thirty six (70.5%) patients received Alendronate therapy. The dosages employed ranged from 10 mg to 40 mg /day. Seventeen (47.2%) of these patients had been treated earlier with calcitonin or etidronate in the past without biochemical remission. Of the 36 patients, 28 received 10 mg of Alendronate per day, three patients received 20 mg/day and five patients received higher doses (30-40 mg per day) at initiation of therapy. Five (13.8%) patients belonging to this group, were lost to follow up. The dosages had to be increased further in 6/31 patients to bring about disease remission. Long-term follow up data (> 2 years) was available for 18/31 patients on low doses of Alendronate and six month follow-up data for 10 patients. At 6 months there was a mean reduction in serum alkaline phosphatase of 40.1% whereas at the end of one year, the mean reduction was 64% (Table 1). In seven patients, alendronate has been discontinued and the serum alkaline phosphatase remains normal after drug discontinuation.

Table 1 : Pre and post treatment values of serum alkaline phosphatase after 1 year of alendronate therapy

Serial no.	S.Alkaline phosphatase (pretreatment) U/L	S.Alkaline phosphatase (post treatment) U/L	% reduction
1.	398	78	80
2.	1319	845	35.9
3.	183	154	15.8
4.	2716	117	95.7
5.	143	74	48.3
6.	197	73	62.9
7.	104	50	51.9
8.	249	72	71.1
9.	158	112	29.1
10.	503	207	58.8
11.	3873	250	93.5
12.	2094	79	96.2
13.	382	72	81.2
14.	318	50	84.2
15.	382	154	59.7
16.	427	182	57.3
17.	565	307	45.7
18.	389	77	80.2
19.	99	60	39.3
20.	1400	99	92.9
			63.98

Two patients, one with a cauda equina lesion and another with severe polyostotic Paget's disease and root pains involving the lumbosacral roots received intravenous Pamidronate at 30 mg per dose initially and were later changed to oral alendronate. Repeat bone scans were available for 16 patients. The scans had shown no new lesions and improvement in some of the preexisting lesions was seen in 14/16 of the subjects. (Fig 3)

Follow up

Fifteen (29.4%) patients never reported after their first outpatient visit. The mean follow up period was 43 months (range 1-156 months). At least 6 months follow up is available in 31 patients, 1 year follow up in 22 patients (47.1%) and longer term follow up that is for more than 2 years in 21 (43.1%) patients. No mortality due to Paget's disease was reported in the current series of patients. However one patient developed a fracture of the humerus while on treatment.

DISCUSSION

Paget's disease of bone is uncommon in India. In a tertiary care referral clinic with a special interest in metabolic bone disease, we found 51 patients over a 8 year period (approximately 6-7 cases per annum). Population based prospective studies are required to provide epidemiological information on the prevalence of this disease but judging from our findings it is likely to be far less common than in Western countries or Australia. Now that people have easier access to health

care services, radiology, radionuclide bone scanning, biochemical testing, Paget's disease may be easily diagnosed provided there is a high index of suspicion.

It is a disease of the elderly as was seen from the current series where the mean age at presentation was 56 years, 37.3% of patients from the age group ranging from 61-70 years. Though it is rare before age 20, we had two patients below 16 years of age. Sex distribution in the Western series is found to be equal but there was a male predominance in our series. This may be due to gender bias in patients seeking medical care in India.

The commonest presenting symptom was localized bone pain followed by low backache, bony deformity, pathological fractures, deafness, skull enlargement, neurogenic claudication, renal stones, painless swelling in that order. The combination of low back pain and elevated serum alkaline phosphatase should arouse clinical suspicion of this rare disorder. Some of the symptoms can be very vague whereas others like fractures, cardiac failure etc. can be disabling. Ten percent of patients were asymptomatic and were referred with an elevated serum alkaline phosphatase. It is likely that with more frequent health evaluation amongst the general public, more subjects would be diagnosed while they are still asymptomatic.

With regards to the disease complications, hyperuricemia was the most common (4/9 being symptomatic) followed by deafness, secondary osteoarthritis and radiculopathy. None of our patients had features of high output cardiac failure nor did any patient develop sarcomatous transformation of the bony lesions. Ninety percent of the patients had polyostotic Paget's disease. The pattern of skeletal involvement was very similar to what has been described in the literature.^{1,8}

Follow up was poor in the initial years of the study, when only Calcitonin and Etidronate were available for treatment. At least 6 months of follow up was available in 31/51(60.8%) patients and longer term follow up in 22 (43.1%) patients (>2 years). The advent of bisphosphonates for the treatment of Paget's disease of bone has made a major difference to the outcome. They are non-hydrolyzable analogues of inorganic pyrophosphate, that bind to hydroxyapatite and inhibit osteoclast-mediated bone resorption. This is followed by a secondary decrease in bone formation. Currently, five bisphosphonates are approved by the US Food and Drug Administration for the treatment of Paget's disease including pamidronate, which is given intravenously, and etidronate, tiludronate, alendronate and risedronate, which are all taken orally.

With the introduction of bisphosphonates, there was a considerable improvement in the compliance rates and follow-up owing to ease of availability and reasonable cost. Fifteen (30%) patients in our series were lost to follow up. Long term follow-up data are available for twenty two (47%) of patients.

One of the striking observations in our study was the good clinical response seen to smaller doses of Alendronate. The recommended dose of Alendronate in literature is 40 mg/day for a period of 6 months followed by a drug-free period. However, of the 36 patients on Alendronate therapy, 31(86%) received smaller doses (10-20 mg/day). The mean reduction of 40% in serum total alkaline phosphatase levels after 6 months of therapy and 64% reduction at the end of one year in patients who received smaller doses of Alendronate in the present study suggest that lower doses are often adequate. Only a minority of these patients needed higher doses of alendronate later on to improve the biochemical response. Considering that alendronate is deposited in the skeleton and stays deposited for years, it is not surprising that lower doses of alendronate should suffice. This may have the advantage of fewer adverse events, improved tolerance to the drug and improved patient compliance.

Reid *et al.*¹² mention two recently completed long-term, randomized, double-blind, multicentre, controlled studies in which men and women with moderate to severe Paget's disease received oral alendronate 40 mg daily for 6 months. One study compared the effects of alendronate 60 mg/day with those of oral etidronate 400 mg/day; the other compared the effects of alendronate with those of placebo. In both studies alendronate significantly reduced serum concentrations of alkaline phosphatase by more than 70%, which was significant in comparison with the baseline alkaline phosphatase levels in the other regimens. We were able to achieve a similar reduction in serum alkaline phosphatase over a one year period of lower dose alendronate therapy.

At least one measurement of bone metabolic activity and x-rays / bone radionuclide scans of affected bones are recommended to monitor the response to treatment in patients with Paget's disease. While several markers of disease activity such as urinary hydroxyproline/creatinine, urinary and serum deoxypyridinoline, N-telopeptide and C-telopeptide have been studied in the past, none of them is readily available in developing countries nor do they offer major advantage over serum alkaline phosphatase. Serum alkaline phosphatase, a marker of osteoblast activity which is readily available in most laboratories is a good marker of disease activity in Paget's disease of bone.

CONCLUSIONS

In conclusion, Paget's disease of bone does occur in our population though the prevalence may be lower than in the West. One has to consider this possibility in the differential diagnosis in patients with low back pain and elevated serum alkaline phosphatase. The pattern of skeletal involvement is similar to what is published in the literature. If left untreated, Paget's disease of bone

can lead to complications such as pathological fracture and cardiac failure which can increase morbidity and mortality. Oral alendronate is a simple form of treatment and about half as doses what has been recommended may suffice. However if one adopts this approach, the treatment duration may have to be extended to 1 year to achieve a similar biochemical response in terms of reduction in serum alkaline phosphatase. There is a need to conduct a prospective randomized controlled study to determine the minimum dose of alendronate that would be effective in the treatment of Paget's disease. Intravenous Pamidronate may be required in patients with neurologic sequelae to obtain a more rapid response and to prevent neurologic disability. With increasing medical awareness, increasing longevity and with more people going in for routine biochemical tests, this disorder is likely to be diagnosed earlier in more patients.

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API Announcement



Election for Posts of API and ICP

Election process is on for the following posts of API and ICP for the year 2007-2008:

President Elect	1
Vice President	1
Hony. General Secretary	1
Governing Body Members	4
Faculty Council ICP Members	5

Ballot papers for these elections shall be sent to all the members by **15th July, 2006** and same need to be sent back to API Office by **31st Aug, 2006**.

In case a member does not receive the ballot paper by **1st Aug, 2006**, he/she can send a written request under his/her signature to API Office at the address given below so that duplicate ballot paper can be sent to them.

The Association of Physicians of India, Turf Estate # 6 & 7. Off. Dr. E. Moses Road, Opp. Shakti Mills Compound, Near Mahalaxmi Station (West), Mumbai-400 011. Fax: 022-24920263

(Dr. R. K. Singal)
President Elect &
Chief Electoral Officer

(Dr. Falguni S. Parikh)
Jt. Secy. API