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A Classic Case Report On Paget's Disease Of Bone

Sharon Susan Raj[1], Archana Rajan[2], Rintu Mary Roy[2], Philip Finny[3], Saidheer. D[4]

[1]*Pharm.D Intern, Karnataka College of Pharmacy, Thirumenahally, Hegde Nagar,Bengaluru - 560024*
[2]*Pharm.D Intern, Nazareth College of Pharmacy, Othera,Thiruvalla, Kerala.*
[3]*Senior Consultant and HOD, Department of Endocrinology, Believers Church Medical College Hospital, Thiruvalla, Kerala.*
[4]*Vikas College of Pharmaceutical Sciences, Jawaharlal Nehru Technological University, Hyderabad, India*

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ABSTRACT: Everything has got its adaptive potential from the primitive variety of prokaryotes to the extreme model of eukaryotes. The photosensitive eyes, the touch-sensitive Mimosa pudica, and yes! even Paget's disease of bone has got its tale of adaptation. With 126 appendicular skeleton bones, 74 axial skeleton bones, and 6 auditory ossicular bones, the skeletal system undergoes modelling as well as remodeling in adapting to external signals and retaining the bone strength respectively. (1). One of the key processes involving bone homeostasis is bone remodeling. The dynamic skeletal organ system, even after reaching its maturity, continuously undergoes periodic replacement of the old with the new. The dysregulation of which can lead to a variety of skeletal diseases including Paget's. (2)

Though up to 40 % of the patients with Paget's disease present with bone pain, Paget's disease is often asymptomatic initially and is usually diagnosed with radiographic images of its classic features. An early diagnosis of which can put a barrier over complications such as arthritis, hearing loss, heart failure, other neurological complications, etc. Calcium and phosphate levels are seen to be within the normal range whereas there is a significant feature of elevated alkaline phosphatase in almost every patient. Many treatment options like bisphosphonates have shown a reduction in bone turnover and have brought normal bone turnover indices to the disguise of the patient's life quality. (3)

KEYWORDS: Paget's disease, osteoarthritis, alkaline phosphatase, bisphosphonates, bone turnover

I. INTRODUCTION

Paget's disease is a chronic uncommon bone disorder, which has a predilection towards the male gender against the female and is seen in a 3:1 ratio (4). It is more commonly seen in the Anglo-Saxon population and is relatively rare in India. (3) Apparently, it has been nearly one and half centuries after Sir James Paget described the disease initially in 1877. Based on his belief that Paget's disease is caused due to chronic inflammation, it was coined as "osteitis deformans". (5)(6) Paget's disease of bone is the most common metabolic bone disorder after osteoporosis. It is sometimes of monostotic or polyostotic origin. This disease occurs when osteoblasts form a disorganized bone structure succeeding dysregulated bone resorption by the multinucleated osteoclasts. Although any bones can be affected, the proclivity of the disease is mainly towards the axial skeleton, say, the spine, pelvis, femur, sacrum, and skull. (7)

II. CASE REPORT

A 60-year-old male came for evaluation of bone deformity, which he had for 15 years. He also presented with complaints of hearing loss and temporomandibular joint discomfort. He had swelling and hyperpigmentation on the left leg and he was evaluated for the same in a tertiary care hospital. The biopsy was verbally told to be normal and no records were available. In 2012, he was diagnosed with osteoporosis and had taken bisphosphonates. He was also recorded as being treated for osteomyelitis.

He had h/o right hip bone, femur, and patella fracture due to a road accident. In 2019, December, he was suspected of left leg chronic osteoarthritis and his alkaline phosphatase level was recorded to be 655IU/L. Later he was lost to follow up due to the pandemic.

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In March of 2022, he had an injury to his left leg and was under evaluation by an orthopaedist. He has also diagnosed with Diabetes Mellitus around 1 year ago and is on T. Metformin 500mg 1 - 0 -1. In addition, he had a h/o Coronary Artery Disease, for which he took T. Aspirin and other Ayurvedic medications. This further resulted in the development of severe pain in the left leg. To add on, he has an allergy to multiple drugs including T. Ibuprofen and T. Diclofen. In the context of high alkaline phosphatase levels, Paget's disease was suspected and was referred to the endocrinology department. He was then initiated on T. Alendronate for the past 6 months twice weekly and was being evaluated since then.

Examinations and blood investigations

On his latest follow-up, a Cardiovascular system examination showed a pulse of 88 beats/min and it was essentially regular. His blood pressure was recorded to be 130/80 mmHg and on examination of the respiratory system, his breath sounds were non-vesicular. CNS examination was also found to be normal. Evaluation of the musculoskeletal system revealed anterolateral bowing of the tibia in the left leg.

His blood investigations were within the normal limit including the alkaline phosphatase.

Parameter	Reference range	Result (02/03/22)	Result (25/04/22)	Result (30/04/22)	Result (23/08/22)	Result (26/10/22)
Glucose	65–99 mg/dl	-	165.7	-	151.3	154.2
HbA1c	4 – 5.6%	-	7.4	-	6.9	7
Creatinine	0.76–1.46 mg/dl	-	0.87	-	-	0.97
Sodium	135–146 mmol/l	-	137	-	-	-
Potassium	3.5–5.3 mmol/l	-	4.2	-	-	-
Calcium	8.6–10.2 mg/dl	9.62	9.21	-	-	9.57
Phosphorous	2.5 – 4.5 mg/dl	-	-	-	-	3.53
Vit. D	30 – 100ng/dl	-	39.9	24.3	79.9	-
Albumin	3.6–5.1 g/dl	-	4.25	-	4.45	4.19
Bilirubin, total	0.2–1.2 mg/dl	-	1.16	-	-	-
S. Protein	6 – 8 g/dL	-	-	-	-	7.81
S. globulin	3.5 – 4.8 g/dL	-	-	-	-	4.19
Albumin: Globulin	1-2	-	-	-	-	1.16
SGOT	10 – 40 U/L	-	-	-	-	29
SGPT	10 – 40 U/L	-	47	-	-	32

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Alkaline phosphatase	40–115 U/l	547	-	-	114	94
ESR	0-15 mm/hr	10	-	-	-	-
Hb	12-16g/dl	-	-	16	16.3	
PTH	15 - 88 pg/ml	-	43.4	-	-	34.5
TLC	$(4–11)10^9$/L	$(10.42)10^9$ /L	$(8.1)10^9$ /L	-	-	-
Polycytes	45 – 75 %	65	59	-	-	-
Eosin	0-4%	5	2	-	-	-
CRP	0-10mg/L	3.1	-	-	-	-
Lymphocytes	20 – 50 %	-	-	32	24	-
Monocytes	0-10%	-	-	7	6	-
RBC	4.3 – 5.6 million	-	-	5.22	-	-
PCV	38-48%			47.3	47.5	-
MCV	80-100fL	-	-	90.6	88.7	-
MCH	27-34pg	-	-	30.6	30.5	-
MCHC	31-37g/dL	-	-	33.7	34.4	-
RDW	12.1 – 14%	-	-	13.1	12.6	-
Mentzer Index	15 – 19	-	-	17.36	16.58	-
Platelets	1.5 – 4.5 lakh/10^{-6}L	- -	-	2.16	2.15	-
Mean Platelet Volume	8-11fL	-	-	8.1	9.5	-
Reticulocyte Count	0.5 – 2.5%	-	-	1.36	1.64	-
HDL	40-59mg/dl	-	45	-	-	-
LDL	0-100mg/dl	-	165	-	-	-
Cholesterol : HDL	0-4.5	-	5.38	-	-	-
VLDL	0-20mg/dl	-	46.8	-	-	-

Table1 gives the patient's metabolic work results during the regular follow up

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The Tc bone scan showed diffuse increased uptake in the upper 2/3rd of the left tibia. Chest-X ray and X-ray skull were also within the normal limits and are given in the following figure.

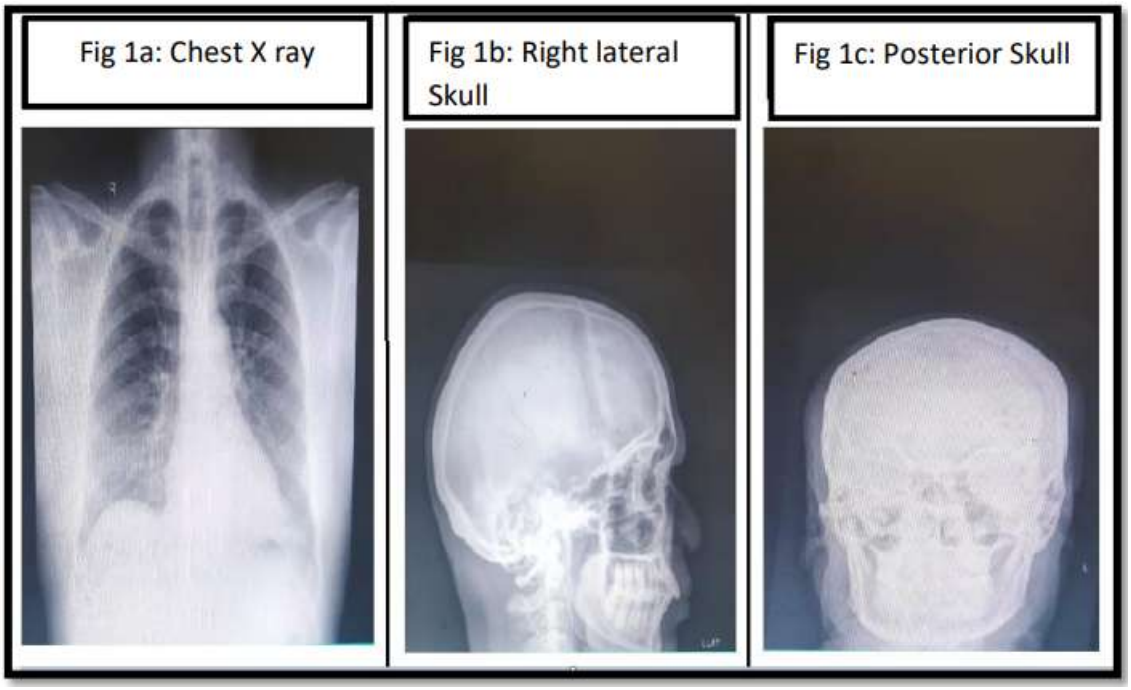

Figure 1: X-ray of chest and skull

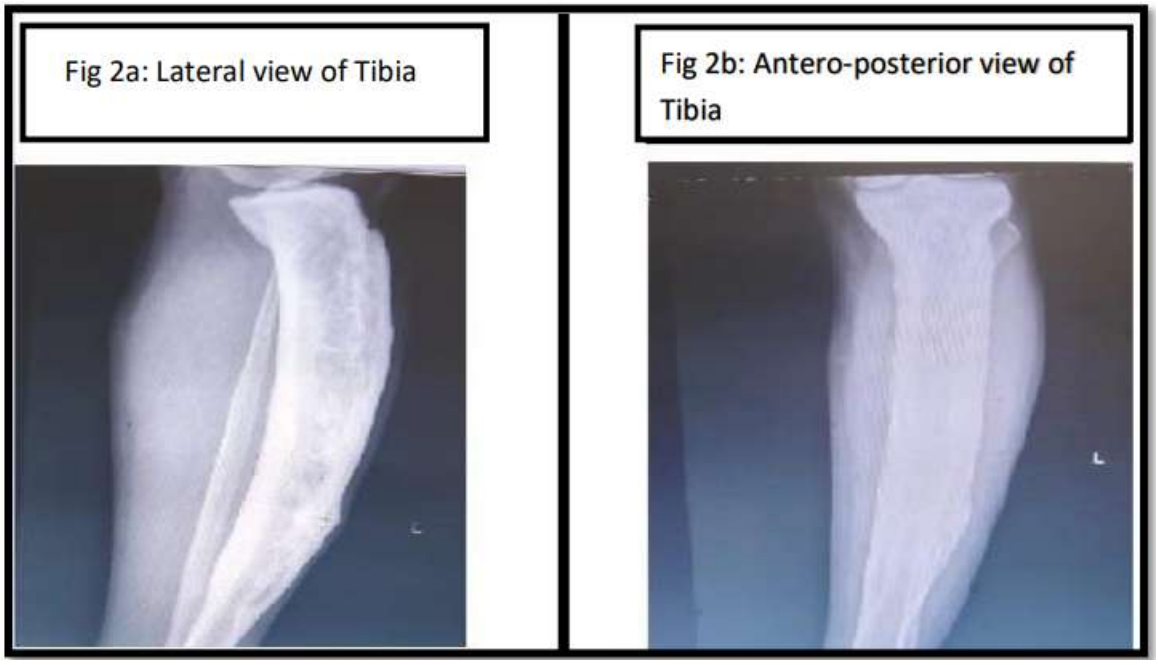

Fig 2: X- ray of left tibia in the antero-posterior axis and lateral axis

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Given the hearing loss, an audiogram was done and the PTA was noticed to be within normal limits with a dip at 4kHz. Dermatology consultation was sought because of progressive hyperpigmentation of both ankles and the dorsum of feet. B/L pitting pedal edema was noticed on standing which was subsequently resolved on lying. On further clinical examination, the patient was observed with blotch hyperpigmentation and induration over the dorsum of the feet. Apart from the above dermatological concerns, Incompetent perforator veins were noted on both GSV and SSV territory of the right lower limb. Chronic venous insufficiency of both lower limbs was suspected and venous doppler studies were advised. In addition, dental consultation was sought in the context of TMJ discomfort and it was within the normal limits. He was advised warm compress with muscle massage 3 times a day for 1 week. ECG and ECHO were also normal.

Treatment

After being on T. Alendronate for the past 6 months, a repeat ALP showed a difference from an initial value of 655IU/L in 2019 to 94IU/L in October 2022. He was also recorded to be symptomatically better.

III. DISCUSSION

Paget disease is the focal increased and dysregulated bone remodeling, which often affects one or more bones in the skeletal system, and Paget's disease of the tibia accounts for 32% of the total types of Paget's disease affecting different bones. (8) The increased prevalence of the disease in particular races certainly talks about genetic predisposition as one of the major etiologies. Despite this, there are a few other conflicting hypotheses as well. The discovery of intranuclear inclusion bodies in the pagetic osteoclasts has given rise to two different experimental paths. Some suggest infection as a potential trigger to the disease due to its resemblance to paramyxovirus nucleocapsids, whereas others talk about the possibility of abnormal protein aggregates resulting from the defects in the autophagy pathway. 15% of the patients with Paget's disease have an autosomal dominant family history and it is estimated that in around 40 to 50 % of the patients with family history as well in 5 to 10% of the patients with the isolated disease, they have a significant mutation in SQSTM1, which encodes for osteoclast regulatory protein named p62. Several other gene mutations clinically present as Paget's disease and are closely associated with the genes regulating osteoclast function.

It is also believed that the proportion of the total population having symptoms before diagnosis is considerably low, say around 5 to 10%. Bone pain is the most predominant symptom, primarily because of increased bone turnover. If Paget's disease affects the skull, deafness also comes along. The other major clinical manifestations include bone deformity and warmth of the skin above the affected bone. Complications of Paget's disease include osteoarthritis, spinal stenosis, obstructive hydrocephalus, high-output cardiac failure, and hypercalcemia if the patients remain immobile.

A radiograph, which briefs the features of focal osteolysis with coarsening of the trabecular pattern, expansion of the bone, and thickening of the cortical areas is often considered the basis for diagnosing Paget's disease. Along with the radiograph, radionuclide bone scans help in figuring out the extent of the disease and if any symptoms develop at locations distant from those seen on radiographs. If spinal stenosis or osteosarcoma is suspected, then MRI or CT is indicated.

Laboratory assessment of renal function, calcium levels, albumin, alkaline phosphatase, and 25-hydroxyvitamin D is done along with liver function tests. The latter is often done to rule out if the elevation in alkaline phosphatase is of hepatic origin. In typical Paget's disease, there is an isolated elevation of alkaline phosphatase.

According to," The Bone Research Society of the United Kingdom", there is relevant significance in using antiresorptive therapy, if the bone pain is clearly due to increased metabolic turnover. To rule out other etiologies of bone pain, the most straightforward case of Paget's is localized bone pain along with elevated alkaline phosphatase level. In the case of bone pain, which gets better at rest and increases weight bearing, osteoarthritis can also be a possible diagnosis. In a such clinical scenario, a therapeutic trial of bisphosphonates can be started to determine if the increased metabolic activity is a possible reason. If else, further evaluation of the causes of bone pain is required.

One of the other distinctive features of the disease is a pseudo fracture. The asymptomatic pseudo fracture can be treated conservatively but surgical stabilization is required in patients with localized bone pain.

Randomized Clinical trials have shown that the use of amino bisphosphonates decreases

bone turn over as compared to simple bisphosphonates and symptoms do improve as the elevated alkaline phosphatase falls under the normal range. Calcitonin is also indicated in patients with localized bone pain due to increased bone turnover if bisphosphonates are contraindicated. Along with antiresorptive therapy, sometimes analgesic agents, anti-inflammatory drugs, and ant-neuropathic agents are used due to their potential in controlling bone pain. (9)

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CONFLICT OF INTEREST: None declared

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