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Case Report

Unraveling Paget's Disease of the Skull and Spine and Therapeutic Response with Bisphosphonate: A Case Report

*Salam MU[1], Hussain I[2], Ahmad MM[3], Haque R[4], Ahmad S[5], Rahman S[6], Alam S[7], Chowdhury NB[8]

Abstract:

Background: Paget's disease of bone is a chronic disorder characterized by abnormal bone remodeling, often leading to structurally compromised bones. Although it can be asymptomatic, involvement of the skull and other bones can cause significant complications. This case report presents a postmenopausal woman with Paget's disease, complicated by iron deficiency anemia and secondary hyperparathyroidism due to vitamin D deficiency.

Case Presentation: A 56-year-old woman with a 12-year history of asthma and hypertension presented with vertigo, a recent fall, and mild headaches. Examination revealed notable cranial deformities and scalp vein dilation. Investigations showed severe microcytic hypochromic anemia, elevated parathyroid hormone, low vitamin D, and high alkaline phosphatase levels. Imaging confirmed extensive Paget's disease affecting the skull and other bones. She was treated for iron deficiency anemia and vitamin D deficiency and received bisphosphonate therapy with intravenous zoledronic acid. Over five years, her biochemical markers normalized, though physical and radiological improvements were minimal.

Conclusion: This case highlights the importance of early diagnosis and long-term management of Paget's disease, particularly when complicated by metabolic disturbances. Comprehensive treatment, including vitamin D supplementation and bisphosphonates, can lead to significant biochemical improvement, although physical changes may persist. Compliance with treatment and regular follow-ups are crucial for successful disease management.

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Introduction:

Paget disease of bone (PDB) is a chronic progressive disease of the bone of uncertain etiology, characterized initially by an increase in bone resorption, followed by a disorganized and excessive formation of bone, leading to pain, fractures, and deformities.[1,2]

1. Mahjuba Umme Salam, Professor and Head, Dept. of Medicine, SWMC, Sylhet*
2. Imran Hussain, Assistant Registrar, Department of Gastroenterology, SOMCH. Ex Assistant Registrar, Department of Medicine, SWMC, Sylhet.
3. Md Masuq Ahmad, Assistant Registrar, Department of Medicine, SWMC, Sylhet
4. Md. Rashedul Haque- Professor and Head, Department of Pediatrics, SWMC, Sylhet
5. Shahed Ahmad- Associate Professor, Department of Medicine, SWMC, Sylhet
6. Sayem Rahman, Registrar, Department of Medicine, SWMC, Sylhet.
7. Shahidul Alam, Registrar, Department of Medicine, SWMC, Sylhet
8. Nazrul Bakth Chowdhury, Registrar, Department of Medicine, SWMC, Sylhet

Corresponding author: Mahjuba Umme Salam
Professor and Head, Dept. of Medicine, SWMC, Sylhet
Email: mahjubasalam@yahoo.com

This condition can manifest as a monostotic or polyostotic disease. Involvement of the skull can result in neurological symptoms such as vertigo, headaches, and cranial nerve compression, which significantly impacta patient's quality of life.[3]Though the exact etiology remains unclear, genetic, viral, immunogenic and neoplastic origins have been postulated. PDB often runs in families, and several genetic mutations, especially in the SQSTM1 gene have been linked to increased susceptibility. There is some evidence suggesting that viral infections (e.g., paramyxovirus) may trigger the abnormal bone remodeling process, though this theory remains controversial.[4,5]It is common in the Anglo-Saxon population, but is relatively rare in India. PDB is

often asymptomatic and is commoner among the aging population.[2,6]Its diagnosis is often incidental, made through imaging studies that reveal characteristic bone changes.[7]Markedly elevated serum alkaline phosphatase (SAP) is a constant feature while calcium and phosphate levels are usually within normal limits.[8] Management typically involves the use of bisphosphonates, a group of anti-resorptive drugs that can decrease morbidity and mortality associated with the disease.[8,9]

This article presents a complex case of Paget's disease in a postmenopausal woman, who had been hypertensive and asthmatic for many years, and then came to special attention due to a fall and subsequent revealing of characteristic radiological features. The diagnosis was then quite straight forward due the presence of the classic features of PDB with craniofacial involvement resulting in Leontiasis Ossea (lion like face), cotton wool appearance of the skull on CT scan of the head and an elevated SAP. However, her condition was complicated by the presence of severe iron deficiency anemia and secondary hyperparathyroidism due to vitamin D deficiency. This case highlights the incidental nature of diagnosis and the slow response to therapy due to interrupted intervention owing to the COVID-19 pandemic.

Case summary:

A 56-year-old housewife and mother of three, with a 12-year history of asthma and hypertension, presented to the outpatient medicine clinic with complaints of vertigo lasting several months and a recent fall. She also reported occasional mild headaches and back pain but denied experiencing loss of consciousness, bone pain, hearing loss, visual disturbances, or tingling and numbness in her limbs. She mentioned occasional chest pain and palpitations but had not experienced ankle swelling, frothy sputum, or orthopnea. She had a history of pallor following excessive menstrual bleeding before menopause, which she entered six years ago. Her current medications included Losartan potassium 50 mg daily for hypertension and a Salmeterol (25 µg) - Fluticasone (250 µg) inhaler, two puffs twice daily for asthma.

On examination, she appeared to have an average build, weighing 50 kg, and was fully conscious. Her pulse was regular, with a large volume, and recorded as 90 beats per minute. Her blood pressure was 160/80 mmHg, with no postural drop. She had notable physical features, including a large head with prominent frontal bossing, prominent cheeks, and a flat nose **(Figure 1-a, b)**. Dilated scalp veins, known as the 'scalp vein sign' **(Figure 1-c)**, were visible on her forehead. There was no localized tenderness over the skull bones, and no warm areas on the scalp were noted. Her breath sounds were vesicular with prolonged expiration, accompanied by a few rhonchi throughout the chest. A precordial flow murmur was detected. Neurological examination revealed no focal deficits. She appeared moderately anemic, though there were no signs of jaundice, purpura, bony tenderness, hepato-splenomegaly, or lymphadenopathy.

Routine blood tests **(Table 1)** revealed a hemoglobin level of 6.5 g/dL and an ESR of 53 mm in the first hour. Although her white blood cell and platelet counts were normal, the MCV (Mean Corpuscular Volume) was 67 fL, the MCH (Mean Corpuscular Hemoglobin) was 18 pg, MCHC (Mean Corpuscular Hemoglobin Concentration) was 26.87 gm/dL and the RDW (Red Cell Distribution Width) was 19.4%. Urinalysis and microscopic examination were normal. Other tests showed a normal serum TSH level of 2.93 µmol/L, creatinine at 0.5 mg/dL, albumin at 4.2 g/dL, and phosphate at 0.99 mmol/L. A peripheral blood smear confirmed microcytic hypochromic anemia with some poikilocytes. The iron profile was consistent with iron deficiency, showing serum iron at 12.4 µmol/L, ferritin at 5.1 ng/mL, total iron-binding capacity at 490 µmol/dL, and transferrin saturation at 2.53%. Lipid levels indicated mild dyslipidemia, with total cholesterol at 220 mmol/L, triglycerides at 201 mmol/L, HDL at 57 mmol/L, and LDL at 123 mmol/L. Serum calcium was slightly low at 8.8 mg/dL, vitamin D3 was deficient at 15 ng/mL, parathyroid hormone was elevated at 269.9 pg/mL, and alkaline phosphatase was high at 960 U/L. A chest X-ray was normal, and a 2-D and M-mode echocardiogram showed a 60% ejection fraction,

with normal chamber and valve dimensions **(Figure 2)**. Abdominal ultrasound results were normal, and a stool occult blood test was negative.

An X-ray skull lateral view showed widened deploic space of the frontal, parietal and, occipital bones with irregular densities **(Figure 3).** An axial CT scan of the head, performed to rule out head injury, revealed normal brain structures but incidentally identified mixed lucencies with osteolytic and osteoblastic areas of bone enlargement and coarsened trabeculae, giving a 'cotton wool' appearance **(Figure 4)** suggestive of Paget's disease of the skull. Fibrous dysplasia was also considered a strong radiological differential. A skull X-ray showed thickened, sclerosed, and irregular skull bones with scattered lucent areas. A Tc-99m HDP bone scan showed increased radiotracer uptake in the skull, several thoracic (specially 3rd and 4th) and lumbar vertebrae, sacral vertebrae, pelvic bones, and both sacroiliac joints **(Figure 5)**.

The patient was transfused with three units of packed red blood cells and started on daily oral iron polymaltose (47 mg) combined with folic acid (0.5 mg) and zinc (22.5 mg) to correct her anemia. Her hemoglobin increased to 10.3 g/dL after the transfusion. Along with treating her anemia, she was diagnosed with secondary hyperparathyroidism due to vitamin D deficiency, and suspected Paget's disease. She was prescribed 1000 mg of oral calcium and weekly 40,000 IU vitamin D supplements for eight weeks, after which she received an intravenous infusion of 5 mg zoledronic acid. She continued daily oral calcium (500 mg) and vitamin D (800 IU) supplements after the infusion.

Annual tests for serum alkaline phosphatase, calcium, phosphate, and parathyroid hormone were conducted. Unfortunately, she was lost to follow-up during the second year due to the COVID-19 pandemic but resumed treatment in the third year with repeated zoledronic acid injections at the end of the third and fourth years. By the fifth year, her serum alkaline phosphatase normalized to 81 U/L, and her levels of serum vitamin D3 (49.9 ng/mL), calcium (9.1 mg/dL), and parathyroid hormone (56 pg/mL) were also within normal limits. Bone densitometry showed improvement **(Figure 6)**, although there was little change in her physical appearance or bone scan findings. Throughout her treatment, adjustments were made to her antihypertensive, lipid-lowering, and asthma medications as needed.

Figure 1: a) large head with frontal bossing; b) flat nose, broad forehead; c) scalp vein sign

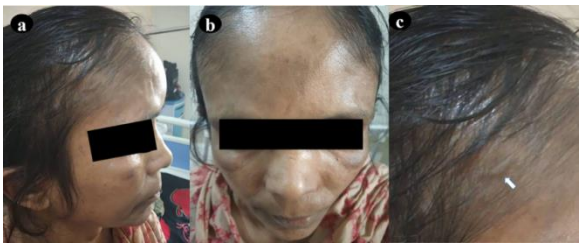

Figure 2: Normal echocardiographic features

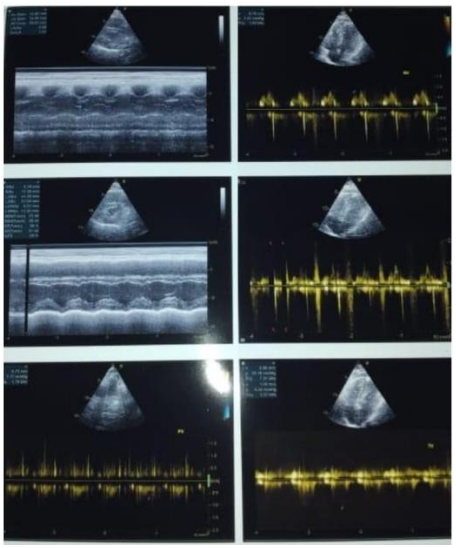

Figure 3: X-ray skull lateral view showing wide deploic space with irregular densities

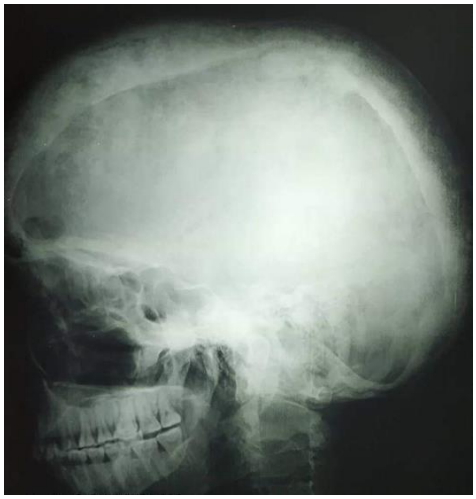

Figure 4: Mixed lucencies of osteolytic and osteoblastic zones (arrow) of bone enlargement and coarsened trabeculae

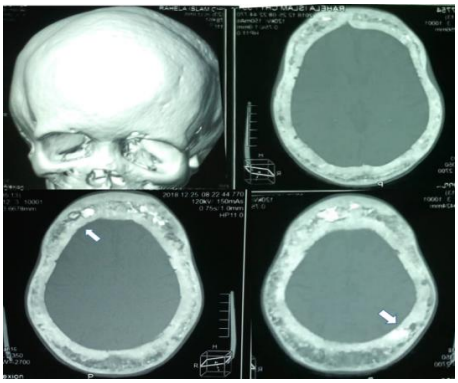

Figure 5: Isotope Tc-99m HDP whole body bone scan showing
increased radiotracer concentration in- a) skull, b) thoracic vertebrae,
c) lumbar vertebrae, d) all sacral vertebrae, e) pelvic bones

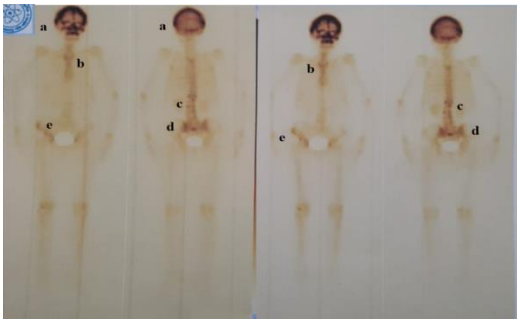

Figure 6: Normal bone densitometry at 5th year

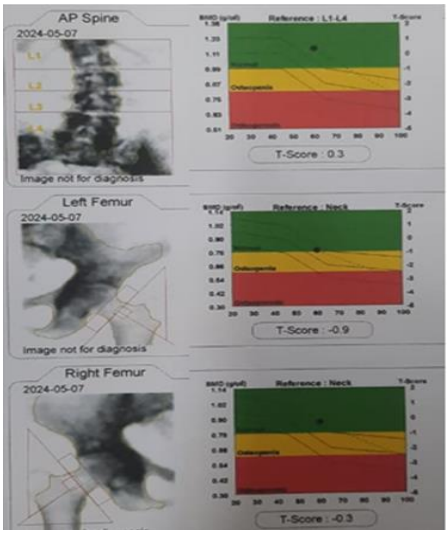

Table 1: Summary of blood test values

	Test parameter	At presentation	At follow up at 5th year
1	**Hemoglobin**	6.5 gm/dl	10.3 gm/dl
2	**ESR**	53mm	40mm
3	**Total count of WBC**	9,000/cu-mm	10,000/cu-mm
4	**Differential count of WBC**	N-60%, L- 35%, M-4%, E-1%, B- 0%	N-64%, L-32%, M-4%, E-0%, B-0%
5	**Platelet count**	1,60,000/cu-mm	2,10,400/cu-mm
6	**Red cell indices**	MCV- 67fL MCH- 18pg MCHC- 26.87 gm/dL RDW-19.4%	MCV- 87fL MCH- 30pg MCHC- 34.48 gm/dL RDW-12.3%
7	**Iron profile**	Serum Iron- 12.4 µmol/L Serum Ferritin- 5.1 ng/mL TIBC- 490 µmol/dL Percent saturation- 2.53%	-
8	**Creatinine**	0.5mg/dl	0.91mg/dl
9	**Electrolytes**	Na- 137 mmol/L K- 4.0momol/L Cl- 102 mmol/L HCO3-22 mmol/L	Na- 135 mmol/L K- 3.6 momol/L Cl- 110 mmol/L HCO3- 23mmol/L
10	**Fasting lipid profile**	TC- 220 mmol/L TG- 201mmol/L HDL- 57mmol/L LDL- 123mmmol/L	-
11	**Serum TSH**	2.93 µmol/L	1.06 µmol/L
12	**Serum parathyroid hormone**	269.9 pg/mL	56 pg/mL

13	**Serum alkaline phosphatase**	960 U/L	81 U/L
14	**ABG**	PH- 7.43 PaO2- 65mmHg CO2-30mmHg HCO3- 22mmol/L	-
15	**Serum albumin**	4.2 g/dL	-
16	**Serum Calcium**	8.8 mg/dL	9.1 mg/dL
17	**Serum phosphate**	0.99 mmol/L	0.82mmol/L
18	**Serum vitamin D_3**	15 ng/mL	49.9 ng/mL
ESR-Erythrocyte Sedimentation Rate, WBC-White Blood Corpuscle, TSH-Thyroid Stimulating Hormone, ABG-Arterial Blood Gas			

Discussion:

Paget's disease of bone (PDB), also known as osteitis deformans, is rare in Asia, Africa, the Middle East, and Scandinavia. Epidemiological trends have demonstrated an increasing prevalence in the United States and, an overall decrease in prevalence in the United Kingdom and other European countries over the past two decades. The disease prevalence increases after 55 years of age in all communities. However, the exact reasons behind such geographical and age distribution are unclear.[6]

Diagnosis is often incidental to radiology or raised alkaline phosphatase levels.[7,11] The reported case, who was in her late fifties, had been seeking medical help for hypertension and asthma for many years until she underwent a CT scan of her head following a fall and it was then only, that the diagnosis of PDB incidentally unraveled. Such incidental diagnosis in asymptomatic patients is quite common in this condition.[12]

Though bone pain, bone deformities (e.g., bowing of long bones, skull enlargement), fractures, and hearing loss are the common skeletal symptoms, the index patient had minimal symptoms of PDB. Her vertigo might be due to her severe anemia as she had no vestibulo-cochlear problem. However, it could also be due to the involvement of the skull due to PDB. Other than this she had no other symptoms attributable to PDB. Other skeletal sites of involvement she had were the pelvis and, the vertebral bodies without any symptom of involvement. Long bones of the lower limbs are the affected sites, as reported in other cases.[6,13] The severe microcytic, hypochromic anemia that she had, as reflected by her low hemoglobin, reduced MCV, and MCH was most likely due to iron deficiency due to menorrhagia. The patient's persistent symptoms of fatigue and dizziness with a history of recent falls required correction through iron supplementation and packed cell transfusion. Her positive response to treatment was reflected by the rise in hemoglobin to 10.3 g/dL following the packed cell transfusion and the iron supplementation.

The pathogenesis of PDB involves abnormal bone destruction by increased osteoclastic activity followed by disorganized bone formation by osteoblastic activity, resulting in structurally weak and deformed bones. Some have described three stages of pathogenesis, i.e. the lytic stage (due to osteoclastic activity), the mixed stage (both osteoclastic and osteoblastic activity), and the inactive stage (due to osteoblastic activity). The pathological fractures of the affected bones take place during the lytic stage and also in the mixed stage due to the formation of large, deformed, and disorganized bones. The disease manifestations gradually decline in the inactive stage.[14]This forms the basis of therapy with bisphosphonates that induce remission through enhanced osteoblastic activity.[15]

The diagnosis of Paget's disease of bone (PDB) primarily relies on the radiological and biochemical findings. In this patient, an early CT scan of the head, performed for an unrelated reason, incidentally revealed characteristic features of PDB.[6] Typically, CT or MRI scans of the skeleton are not necessary after plain X-rays have been used for diagnosis. However, CT scans can be useful for identifying fractures, and MRI scans can detect missed malignant lesions such as sarcomas, giant cell tumors, or metastases within the pagetic bone.[8,16] X-rays are important primary investigations as they can reveal PDB by a number of radiological features like osteolytic/osteosclerotic areas, thickened cortex/ trabeculae and bone expansion/deformity. In the index case, plain X-ray skull was doneon purpose after the CT scan,

and the both of themrevealed features of PDB. As a result, the classical radiographic signs of PDB, such as the 'picture-frame vertebra' or the 'ivory vertebra' in the spine, or the 'brim sign' in the pelvis, were not explored. [8,16,17]

While the radionuclide bone scans or scintigraph offer greater sensitivity as compared to plain radiographs, they have lower specificity in diagnosis. The low specificity of this test is because of its failure to differentiate between bone metastasis, metabolic bone disease and, fibrous dysplasia.[12,15] The index case was diagnosed with the help of combined typical features in CT scan and bone scan. Fibrous dysplasia was a strong differential according to the CT scan features. However, scintigraphy revealing a well preserved bony outline favored the diagnosis of PDB. Smith *et al* found that more than 70% of the symptomatic patients with positive scintigraph have normal bone radiograph.[18,19]

Among biochemical markers, serum alkaline phosphatase (ALP) is the marker of choice, as its elevation correlates with disease severity and activity. This test is also very cheap and widely available.[14,20]Serum osteocalcin, a marker of bone formation, is not recommended for diagnosis or prognosis in clinical practice. More recently, the bone formation marker P1NP and bone resorption markers such as N-telopeptide or C-telopeptide have been considered better alternatives to total ALP. Serum calcium and phosphate levels are usually within normal ranges in the PDB. Sometimes there are minimally decreased calcium and elevated parathyroid hormone levels.[8,21] The index case had a complicated scenario of mild hypocalcemia, hypovitaminosis D and hyperparathyroidism.

The treatment strategy of PDB has changed with the development of potent and effective drugs. At present, treatment is indicated for both symptomatic and asymptomatic patients with active disease and with risk of complications. Considering the involvement of weight-bearing vertebrae, the index patient was subjected to bisphosphonate therapy. In 90% of cases ALP levels normalize within the first year after therapy.[21,22] But the reported case was slow to respond. This might be due to the interrupted follow-up due to the COVID-19 pandemic or may be due to other existing metabolic derangements in the patient. Though subcutaneous injection of salmon calcitonin has been approved as a treatment for PDB, it is rarely used now.[23]

Conclusion:

This case report demonstrates the complexity of managing multiple interrelated conditions in an elderly patient, particularly the interplay between Paget's disease, vitamin D deficiency, and iron deficiency anemia. Paget's disease, although often asymptomatic, can present with complications when the skull is involved, such as vertigo and headaches. Early diagnosis and appropriate treatment with bisphosphonates and vitamin D supplementation can lead to significant biochemical improvement, although physical and radiological changes may persist.

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