

Intermediate Type of Juvenile Paget's Disease: A Rare Case in Indian Population

Abstract

Juvenile Paget's disease (JPD), a rare genetic skeletal disorder characterized by accelerated bone turnover with elevated levels of serum alkaline phosphatase, presents in early childhood. We report a female patient with typical features of JPD with dental finding who remained undiagnosed until 18 years of age. Scarcity of this disease in the Indian literature and need for timely diagnosis to avert progression of disease thus incited us to report this case.

Keywords: *Alkaline phosphatase, Juvenile Paget's disease, osteoprotegerin*

Introduction

Paget's disease (PG) is a rare, chronic progressive disease involving the bone.^[1] PG is a geriatric disease involving 3%–4% of the population occurring above fifth to sixth decade.^[2] In contrast, Juvenile Paget's disease (JPD) is rare with a few cases reported in literature.

In 1958, term JPD was first described in an 11-year-old boy. JPD is a rare autosomal recessive metabolic bone disease, which occurs during first 2 years of life with male predilection.^[3] The disease is characterized by a generalized increase in bone turnover secondary to enhanced osteoclastic activity, skeletal deformity, bone expansion, bone pain, and increased risk of pathological fractures with elevated serum alkaline phosphatase level.^[4]

The present article describes a case report of 18-year-old female presented with distinctive features of JPD.

Case Report

An 18-year-old female patient reported to our institution with complaints of bleeding gums and swelling on the right side of the lower jaw for 6 months. Swelling was slow in growth, started as peanut size, and eventually increased to present size. There was no history of pain associated with swelling. The patient gave a history of progressive hearing loss from 2 years and multiple bone fractures up to thirty in

the limbs spontaneously for minor injuries from childhood. The medical history and family history were noncontributory.

On clinical examination, patient had short stout appearance with bowing of the upper and lower limbs [Figure 1a]. Extraoral examination revealed unilateral facial asymmetry. Intraorally, bony prominence of the mandible extending from 43 to mesial aspect of 47 measuring about 2 cm × 1 cm was noticed [Figure 1b]. The swelling was well circumscribed, nontender, and hard in consistency. Mucosa over the swelling was slightly erythematous. Lymph nodes were not palpable. Based on clinical features, differential diagnosis of Paget's diseases, osteomalacia, and osteoporosis was considered.

Orthopantomogram revealed mixed radiopaque and radiolucent lesion with ground glass appearance and deformed left condylar region with impacted 33 and missing 45 with over retained 85 and accentuated pulp space in relation to 17, 25, 26, 27, 28, 36, 37, 46, 47 [Figure 2]. Skull radiograph revealed bone expansion and lytic areas in the skull vault and mandible [Figure 3a]. Radiograph of the lumbar spine including pelvis showed scoliosis, expansion of bone in pelvis region, and osteolytic and sclerotic areas [Figure 3b].

Serum calcium and phosphorus levels were within normal limits, but alkaline phosphatase was increased up to 182 U/L.

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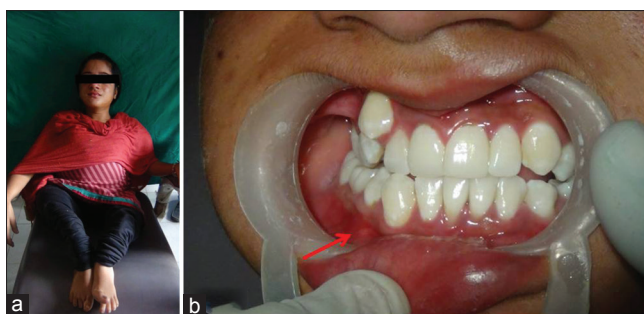


Figure 1: (a) Clinical photograph showing stout appearance with bowing of upper and lower limbs, (b) clinical photograph showing bony prominence (red arrow) in the mandible extending from 43 to 47



Figure 2: Orthopantomogram showing mixed radiopaque and radiolucency appearance and deformed condylar region with impacted 33 and missed 45 with over retained 85 and accentuated pulp space in relation to 17, 25, 26, 27, 28, 36, 37, 46, 47



Figure 3: (a) Posterior–anterior view of the skull showing bony expansion and lytic areas in the skull vault and mandible, (b) X-ray of the lumbar spine and pelvis showing scoliosis with expansion of pelvic bone with osteolytic and sclerotic areas

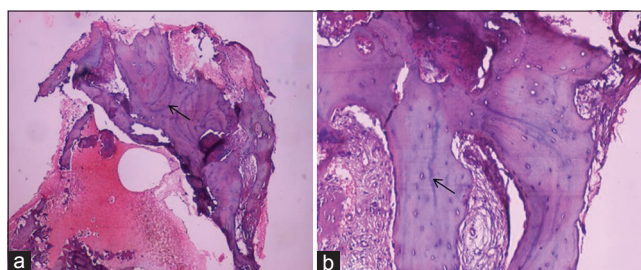


Figure 4: (a and b) Photomicrograph showing interconnecting bony trabeculae with irregular cement lines (black arrow) and loose fibrovascular tissue within the intertrabecular space

Based on investigations, provisional diagnosis of Paget's diseases was considered.

Incisional biopsy was done on the right side of the mandible with respect to 46 region.

Histopathological features showed irregular interconnecting trabeculae with prominent basophilic lines arranged irregularly, which are lined by active osteoblasts and few osteoclasts [Figure 4a]. Resorbed bone and marrow spaces were seen to be replaced by fibrovascular connective tissue [Figure 4b]. Correlating the clinical history, radiographic features, biochemical findings, and histopathological features, final diagnosis of JPD was given.

After a consult from a physician, calinta max (ibandronic acid and calcium tablet) was started for the patient and being evaluated periodically.

Discussion

Paget's disease is essentially a disease of adults presenting in fourth and fifth decades. However, JPD occurs in early childhood.^[3] JPD impairs bone growth but greatly

accelerates remodeling of entire skeleton.^[5] Swoboda coined the term JPD in 1958 to accentuate the similarities between congenital hyperphosphatasia and Paget's bone disease. Both disorders are characterized by bowing of the extremities, increased serum alkaline phosphatase activity, elevated urinary hydroxyproline levels, and abnormal cortical remodeling of highly vascularized bone. The critical event in JPD is thought to be obstacle in the transformation of coarsely woven bone into mature lamellar bone.^[2] This results in an inherently weak skeleton with the reduction of diaphyseal cortices.^[6]

Most accepted pathogenesis is mutation in tumor-necrosis-factor receptor superfamily member 11B (*TNFRSF11B*) gene encoding osteoprotegerin (OPG) including missense defects, insertions/deletions, and frame shifts, thus inhibiting osteoclastogenesis.^[5,7,8]

JPD is a fifth phenotype disorder of constitutive receptor activator of nuclear factor kappa B (RANK B) activation; therefore, JPD due to deficiency of OPG is called as "JPD1" and due to RANK deficiency is called as "JPD2."^[5]

Clinically, JPD is characterized by widespread skeletal involvement in childhood, resulting in progressive deformities such as scoliosis and bowing, short stature, growth retardation, progressive macrocephaly, and facial deformity; mainly maxillary expansion, bone pain, increased risk of pathological fractures, and sensorineural deafness;

and sometimes dermal pigmentation.^[2,3,6] Above-mentioned clinical features are in accordance with the present case. Only few case reports have described dental findings such as missing incisors, resorbed or loose teeth, loss of lamina dura, premature exfoliation of deciduous teeth, or delayed eruption of the dentition.^[2,5,9] The present case showed impacted 33 and missed 45 with over retained 85.

Pathogenesis of Juvenile Paget's disease

The cause of JPD is deficiency of OPG encoded by *TNFRSF11B* gene and is now recognized as a critical regulator of osteoclastogenesis. Regulation of bone turnover is maintained by OPG/RANK-L/RANK system. RANK is regularly expressed on osteoclast precursors and interacts with its ligand RANK-L, thereby stimulating cell to result in differentiation to form active and mature osteoclasts. OPG is a member of *TNFRSF*, soluble, homodimeric, decoy receptor secreted by osteoblasts, binds to RANK-L preventing stimulation of osteoclastogenesis. Deletion or mutations of *TNFRSF11B* gene lead to functional deficit, or mutated OPG results in accelerated bone resorption through the unimpeded interaction of RANKL with RANK, and the rapid rate of bone formation is secondary to the increased rate of bone resorption. The bone laid down is structurally abnormal and develops progressive deformity during growth, thereby resulting in JPD.^[4,7,8]

Phenotype classification

The clinical severity of OPG deficiency seems predictable from the anticipated effects of the specific homozygous *TNFRSF11B* mutation on OPG function. The phenotype classification is based on type and location of mutation in *TNFRSF11B* gene [Table 1].^[4,5,7]

Table 1: Phenotypic classification with mutations

Phenotype classification	Clinical features	Mutation
Severe	Onset of deformity recognized in first 18 months of life walking not achieved at all or delayed and not maintained for the past 5 years Height less than the third percentile	Mutations affecting cysteine residues that were predicted to cause disruption of the ligand-binding region
Intermediate	Onset of deformity recognized after 2 years, walking started at normal age, progressive deformity through growth Height less than the third percentile	Mis-sense mutations not affecting cysteine residues in the ligand-binding domain
Mild	Deformity recognized after 2 years, normal mobility Height within normal range	Insertion/deletion mutation at the C-terminal end of the protein

Imaging in JPD includes X-ray, computerized tomography, magnetic resonance imaging of the skull, spine, pelvis, and long bones, and radionuclide bone scan. Imaging of affected bone typically shows cortical thickening with a coarse, thickened trabecular pattern with osteolytic and sclerotic areas, whereas long bones show deformity such as bowing, fractures, sometimes even vertebral compression fractures, and scoliosis. Imaging of the skull shows increased thickness of skull vault and expansion of jaw bones with osteolytic and sclerotic areas.^[7,9-12] Involvement of the paranasal sinus in JPD is extremely rare.

Biochemical investigations show normal levels of serum calcium, phosphorus, and uric acid with increased levels of serum alkaline phosphatase, acid phosphatase, and urinary hydroxyproline.^[9,12,13]

Histological findings include numerous interconnecting woven to lamellar bony trabeculae lined by active osteoblasts and osteoclasts with prominent cemental lines arranged irregularly, but not characteristic pagetoid or mosaic pattern. Marrow space will be replaced by intervening highly vascular, loose hypocellular, and fibroblastic stroma.^[5,6]

In contrast to Paget's disease, there is excessive surface osteoclasia with classic mosaic pattern with mutations in sequestosome (*SQSTM1*) gene, and in fibrous dysplasia, insufficient osteogenesis within fibrous tissue is noted, except for the absence of a continuous bony trabeculae meshwork.^[6]

JPD is considered to have severe morbidity. If left untreated, most of the children become wheelchair bound at early age.^[3] First line of target is to inhibit osteoclastogenesis, which is important in regulation of bone remodeling. Administration of calcitonin is associated with normal bone formation by decreasing bone resorption and increasing bone mineral content.^[7,12] Recently, subcutaneously administered recombinant OPG, monoclonal antibody that binds with high affinity and specificity to RANK-L, preventing the binding of RANK-L to RANK could be a valuable treatment. Treatment with bisphosphonate (pamidronate) may be equally effective.^[11] Newly, the anti-RANKL monoclonal human antibody has been specified for JPD1 as a "substitute" for OPG.^[5]

Conclusion

JPD is a rare entity in Indian scenario; however, when it occurs, it presents with severe bone deformity. Here, we reported a case of JPD in 18 years aged female patient. Our diagnosis was based on clinical, radiographic, biochemical, and histopathological features. The disease has started at early age and gone unnoticed till now. The disease might mimic others bone diseases, so proper patient history and investigations should be taken into account for proper diagnosis.

As patient gave history of bone deformity and fractures in early childhood and correlating with other investigations, we diagnosed the case as JPD.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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