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Case Report

Cathepsin K Mutation—A Subtle Clinical Presentation

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Abstract

Context: Pyknodysostosis is an uncommon inherited disorder associated with consanguinity, often presenting with sclerotic bone disease, short stature, dysmorphic features, and recurrent fragility fractures at an early age.

Case: A 34-year-old woman was evaluated for the cause of recurrent fragility fractures. She was born of a third-degree consanguineous marriage and had a twin brother who was of short stature. The index patient had a height of 141 cm, dysmorphic features including frontoparietal bossing, blue sclera with short stubby fingers and toes. Radiological evaluation revealed diffuse osteosclerosis with acro-osteolysis exclusively in the toes, apart from mid-facial hypoplasia, lack of pneumatization of the paranasal sinuses, dental abnormalities, and scoliosis. Dual-energy x-ray absorptiometry revealed increased bone mineral density. Based on the clinical features, the patient was tested for cathepsin *K* gene variants using next-generation sequencing and was found to be positive for a novel homozygous c.224T>C, p.Met75Thr likely pathogenic missense variant.

Discussion: This patient presented at a later age than expected with recurrent fragility fractures and the diagnosis was not suspected till adulthood, owing to the subtle clinical features. Confirmation with genetic testing helped in establishing the diagnosis.

Conclusion: Pyknodysostosis, although uncommon, is one of the differential diagnoses for diffuse osteosclerosis presenting with recurrent fragility fractures. Next-generation sequencing in an appropriate setting may confirm the diagnosis.

Key Words: pyknodysostosis, cathepsin *K* gene, osteosclerosis, acro-osteolysis, next-generation sequencing

Introduction

Pyknodysostosis is an uncommon autosomal recessive disorder characterized by a defective cathepsin K gene. Cathepsin K is a cysteine protease lysosomal protein expressed in the osteoclasts encoded by chromosome 1q21 and is involved in the degradation of the matrix (type 1 collagen) of bone and cartilage [1, 2].The estimated frequency of the disorder ranges from 1 to 1.7 per million. It was first described in 1962 [3, 4]. We hereby report a case of pyknodysostosis, presenting in a middle-aged woman who was undiagnosed for a long, owing to subtle clinical features, however, genetic testing clinched the diagnosis.

Case Report

A 34-year-old woman was referred for fragility fractures involving the left and right femur at the age of 27 and 34 years, respectively, following a trivial fall. Both fractures were fixed by open reduction followed by internal fixation using intramedullary nailing. She was born of a third-degree consanguineous marriage without significant antenatal or postnatal history with normal milestones and average scholastic performance. She had a twin brother who was short-statured, with a history of fractures in the past. She attained menarche at the age of 13 years and had regular menstrual cycles. Her height was 141 cm and her weight was not measured owing to a recent right femoral fracture. She was found to have light blue sclera, frontal bossing, asymmetric face with left zygomatic hypoplasia, and short stubby fingers and toes (Fig. 1). Dental examination revealed unerupted teeth (in positions 38, 48, and 13), retained deciduous tooth (position 53), screwdriver-shaped central incisors with midline diastema, high arched palate, and bimax protrusion with class 1 malocclusion. The cranial sutures were also fully fused. The features were subtle and only evident on very careful examination.

Laboratory tests revealed a normal metabolic profile, including a serum sodium (139 mmol/L), serum potassium (3.9 mmol/L), serum corrected calcium (8.9 mg/dL), serum phosphorus (3.7 mg/dL), venous bicarbonate (23 mmol/L), serum chloride (104 mmol/L), alkaline phosphatase (74 U/L), serum creatinine (0.66 mg/dL) that were within normal limits. Her 25(OH) vitamin D (11.9 ng/mL) was low. Procollagen type I intact N-terminal pro-peptide (P1NP) (38 ng/mL) and beta cross-laps (525 pg/mL) were within normal limits. Her skeletal survey revealed diffuse osteosclerosis and acro-osteolysis of the toes but not in the hands (Fig. 2). Her skull x-ray revealed mid-facial hypoplasia and lack of pneumatization of the paranasal sinuses (Fig. 3). She was also found to have mild scoliosis. The bone mineral density (Hologic, Horizon DXA system, CV for lumbar spine: 1%-2%) was elevated with global, lumbar spine, and distal one-third radius density of 1.9, 1.3, and 0.730 gm/cm^2,

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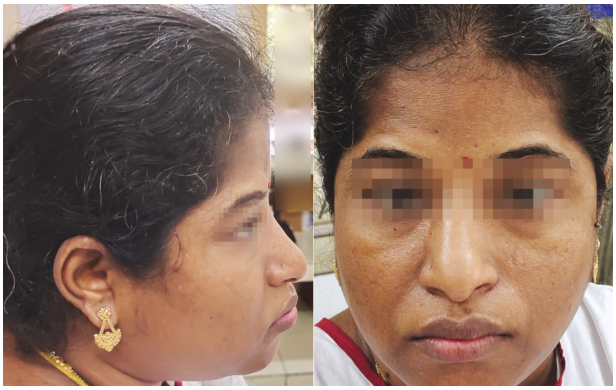

Figure 1. Clinical image showing subtle facial dysmorphic features.

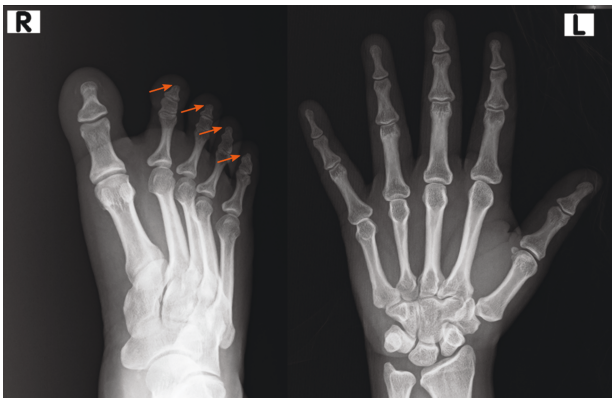

Figure 2. X-ray of the foot showing acro-osteolysis in the toes (denoted with the arrows); the hand does not reveal acro-osteolysis in the fingers but reveals osteosclerosis.

respectively. The corresponding Z scores at the lumbar spine and distal one-third of the radius were +2.8 and +1.0 respectively. Her bone scintigraphy done using a Technetium-99 methylene diphosphonate (MDP) was normal. Histopathological examination of the bone from the fracture site revealed spicules of undecalcified bone admixed with hemorrhage, fibrin, and very scanty fibrous tissue. However, we have not performed bone histomorphometry on the biopsied bone.

In view of the subtle clinical features of pyknodysostosis, we performed the mutational analysis utilizing next-generation sequencing of the targeted amplicons of the *CTSK* gene which revealed a novel homozygous *CTSK* gene missense mutation (NM_000396.4): c.224T>C, p.Met75Thr (Fig. 4). This variant has not been reported in the gnomAD database and the majority of the in-silico tools predicted a pathogenic outcome. Based on American College of Medical Genetics and Genomics (ACMG) 2015 guidelines, the variant has been classified as a likely pathogenic variant, confirming the diagnosis of pyknodysostosis. She was advised to follow strict fall prevention measures as there is no specific therapeutic modality that is currently available. Physiotherapy exercises were also taught to the patient for the prevention of further fractures.

Discussion

The classical manifestations of pyknodysostosis include short stature, acro-osteolysis of all distal phalanges, frequent fragility fractures, clavicular dysplasia, and skull deformities with

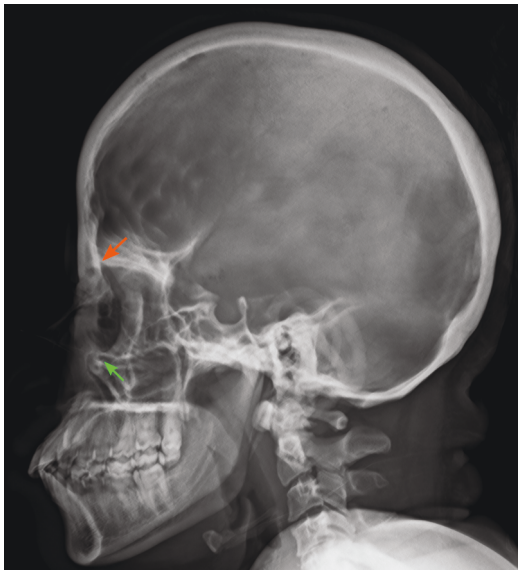

Figure 3. Lateral x-ray of the skull showing mid-facial hypoplasia (shown with an asterisk) with lack of pneumatization of the paranasal sinuses (shown with the arrows).

delayed suture closure [5]. Patients usually attain an adult height ranging between 130 and 150 cm [6].These patients may have low insulin-like growth factor (IGF)-1 secretion [7], and the skull vault is enlarged with a small chin and a beaked nose. Oral abnormalities include mispositioning of teeth, which are prone for dental caries, a high arched hard palate, a long soft palate, and a long uvula. Persistent deciduous teeth with dental crowding can be seen with proptosis and blue sclera. Moreover, these patients may have short limbs, shortish broad hands and feet, and dystrophic nails—clubbing of fingers and toes and grooved nails with asymmetrical acro-osteolysis.

Other features include pectus excavatum, spondylolysis, and kyphoscoliosis [8]. Fragility fractures of the long bones are common, typically healing with deformities [9]. Rarely, pyknodysostosis may be associated with central giant cell granulomas at the maxilla, which could respond to systemic glucocorticoids [10-12]. In a study from India, Sanger sequencing was utilized to characterize a large case series of 25 patients with pyknodysostosis, and causative mutations were identified in all of the study subjects. These patients were found to have consanguinity and positive family history in 65% (13/20) and 45% (9/20) of the families, respectively. The main clinical presentation among these patients includes short stature and fractures in 96% (24/25) and 32% (8/25) respectively. Hypoplasia of distal phalanges (acro-osteolysis) was observed in 19/23 individuals (82.6%). An open anterior fontanelle was seen in only 15/25 (60%) patients. The variant that has been reported in our patient was not reported in the previous publication on pyknodysostosis from India [13].

In our patient, the bone turnover markers were within normal limits. However, Nishi et al reported significantly decreased crosslinked N- and C-telopeptides of type I collagen (NTX and CTX, respectively) in urine from pyknodysostosis patients [14]. In contrast, a study in a Danish population also revealed a normal plasma procollagen type I intact N-terminal pro-peptide (P1NP) and CTX in 9 out of their 10 patients and elevated bone turnover markers in only 1 patient. The

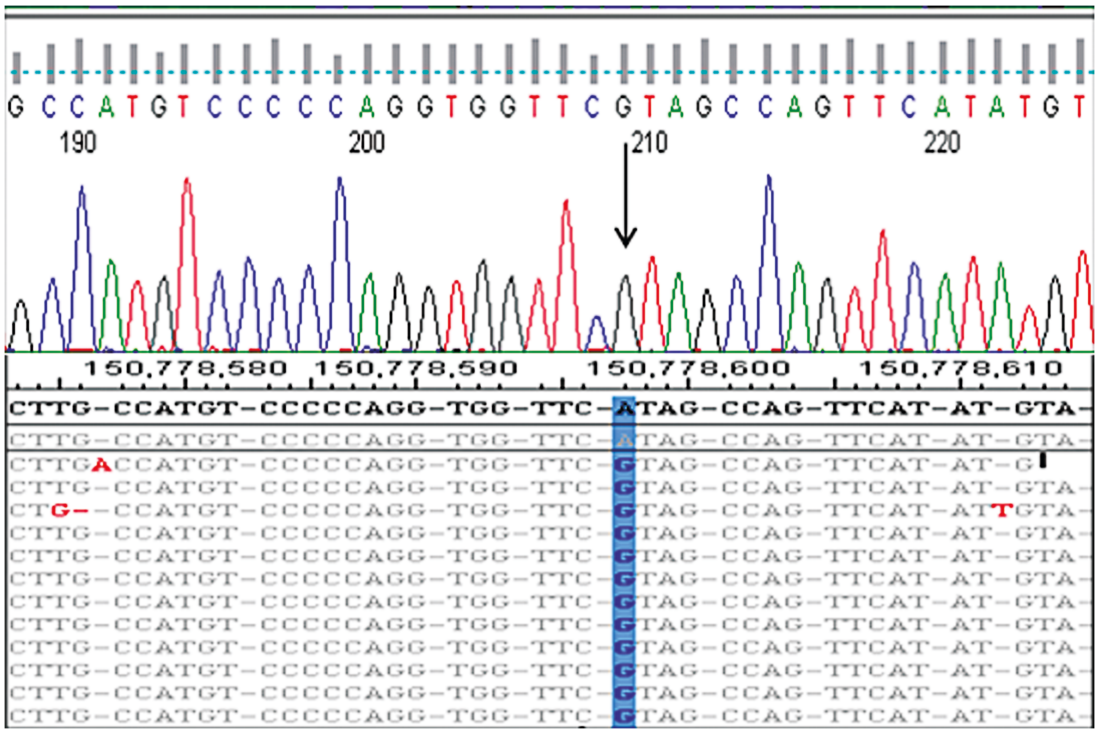

Figure 4. CTSK c.224T>C (p.Met75Thr) Sanger phrenogram and next-generation sequencing.

Table 1. Salient features in inherited osteosclerotic disorders

Dysplasia	Inheritance pattern	Genetics	Onset	Osseous findings	Specific findings
Osteopetrosis	AR, AD	*TCIRG1* (ATP6i), *ClCN7*, *GL* (*OSTM*), RANK-L, *CAII*, *PLEKHM1*	Stillbirth or infancy, adulthood	Diffusely increased bone density; type 1: uniform sclerosis of the skull, spine, long bones; type 2: endo-bone appearance	Still birth, anemia, cranial nerve deficits
Pyknodysostosis	AR	Cathepsin K	Infancy/early childhood	Hyperostosis of long bones, preserved medullary cavities	Dwarfism, acro-osteolysis, Wormian bones
Osteopoikilosis	AD	*LEMD3*	Childhood/ adulthood	Multiple enostoses	Dermatofibrosis lenticularis disseminata
Osteopathia striata	X-linked	Unknown	Childhood/ adulthood	Dense striations in metadiaphyses of long bones	No other associated abnormalities
Progressive diaphyseal dysplasia (PDD)	AD	LAP of TGF-β1	Childhood	Bilateral/symmetric periosteal/endosteal cortical thickening of long bones and/or calvaria	Gait disturbances, pain, weakness
Hereditary multiple diaphyseal sclerosis	AR	Unknown	After puberty	Unilateral/ asymmetric cortical thickening involving long bones only	Milder neuromuscular symptoms compared to PDD
Hyperostosis corticalis generalisata	AR (Van Buchem disease-VBD, sclerosteosis), AD (Worth disease, WD)	SOST, LRP5	Childhood	Endosteal cortical thickening involving long bones, skull, facial bones; mandible enlargement	VBD: facial nerve palsy; sclerosteosis: facial nerve palsy, syndactyly, bone overgrowth; WD: no cranial nerve palsy, torus palatines

Abbreviations: AR, autosomal recessive; AD, autosomal dominant

normal level of CTX in our patient could be related to the recent fractures incurred and the surgery that followed [15, 16]. Overlap syndromes represent disorders of both endochondral and intramembranous ossification with various combinations of hereditary and nonhereditary dysplasia and are highlighted in Tables 1 and 2 [17].

Table 2. Salient features of noninherited and acquired osteosclerotic bone diseases

Noninherited osteosclerotic bone disease			
Dysplasia	**Onset**	**Osseous findings**	**Other features**
Intramedullary osteosclerosis	Adulthood, female predilection	Osteosclerosis limited to medullary cavity, minimal cortical thickening; mid-diaphyseal region of tibia affected	Chronic leg pain increasing with physical activity
Melorheostosis (Leri disease)	Late childhood or early adulthood	Cortical and medullary hyperostosis of a single bone or multiple adjacent bones with a flowing "dripping candle wax" appearance	Pain and stiffness of the involved bones, contractures of the joints, skin changes
Acquired disorders with osteosclerotic bones			
Paget disease	Older than 40 years	Predominantly involve the axial skeleton; polyostotic with asymmetry	Pathologic fracture and neurologic symptoms
Erdheim-Chester disease	40-60 years	Lower extremities, bilateral, symmetric involving diaphysis/metaphysis, sparing epiphyses; cortical thickening, narrowing of medullary cavity, corticomedullary junction loss	Multisystem manifestations: diabetes insipidus, painless bilateral exophthalmos
Myelofibrosis	Middle age to advanced age	Diffuse sclerosis affecting medullary cavity, involving both axial and appendicular skeleton	Anemia, hepatosplenomegaly
Sickle cell disease	Infancy or early childhood	Trabecular thickening and cortical thinning; compression of the vertebral body endplates; Fish-mouth/H-shaped appearance of the vertebral bodies	Premature fusion of growth plates, osteomyelitis/septic arthritis/myonecrosis
Osteoblastic metastases	Late adulthood	Superscan with bone scintigraphy	Carcinoma of the prostate gland, breast, kidney, lymphoma

The cathepsin K gene spans 12 kb and contains 8 exons and 7 introns. Out of 33 mutations in a review, 23 were missense mutations (69.70%), 3 were nonsense mutations (9.09%), 2 were frame-shift duplication mutations (6.06%), 2 were frame-shift deletion mutations (6.06%), 2 were splicing mutations, (6.06%), and 1 was a stop codon mutation (3.03%) [18]. CTSK is secreted into the subosteoclastic space where it efficiently cleaves the peptide bonds of different proteins of the bone matrix, including elastin and type 1 collagen, thereby leading to bone matrix degradation. At present, no specific treatment exists for this disorder. Preventing fractures by taking appropriate measures is essential, and bone healing appears to be normal. Life expectancy may be normal if fractures can be prevented.

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Author Contributions

V.S.N., A.C., and F.K.J. collected clinical data and drafted the manuscript. F.K.J., T.S.J., K.E.C., T.V.P., and N.T. reviewed and edited the manuscript. All authors approved the manuscript for publication.

Disclosures/Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

The next-generation sequencing datasets generated from the case report are not publicly available but are available from the corresponding author on reasonable request.

Informed Consent

Written consent has been obtained from the patient for the use of photographs.

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