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Case Report

Pyle disease (metaphyseal dysplasia) presenting in two adult sisters

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ABSTRACT

Pyle's disease is an extremely rare skeletal disorder characterized by a benign course and an autosomal recessive genetic pattern of inheritance. Its causal mutation is still unknown. In the medical literature, fewer than 30 cases have been described to date. We report the case of two female siblings, daughters of consanguineous parents, referred to the radiology department complaining of genu valgum. Laboratory tests showed no other relevant findings. Conventional radiography plain films revealed Erlenmeyer flask deformity in bilateral femorotibial metaphyses, metaphyseal flaring of long bones, and mild sclerosis of the skull base. The clinicoradiological dissociation, along with the characteristic imaging findings, was consistent with the diagnosis of Pyle's disease. Intervention is not required in most cases, but orthopedic treatment may be required for genu valgum or fractures. Therefore, these cases emphasize the pivotal role conventional radiography plays in the correct diagnosis of this rare entity, allowing for appropriate genetic counseling.

Introduction

Pyle's metaphyseal dysplasia is a rare genetic skeletal disorder of benign course, inherited in an autosomal recessive pattern, whose causal genetic mutation is still unknown [1,2]. Edwin Pyle, an American orthopedic surgeon, first reported the disease in 1931, describing bone deformities involving the skull and limbs of a 5-year-old child [3,4].

There is striking clinicoradiological dissociation, with mild clinical manifestations. Genu valgum is the most common

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feature on physical examination and is frequently the only consistent finding [1]. Other findings that may be observed on physical examination include bilateral and symmetrical enlargement of the knee, proximal two-thirds of the humerus, distal two-thirds of the radius and ulna, as well as the proximal phalanges and distal metacarpal bones [3,5,6]. Other clinical manifestations include caries, poor dental implantation, malocclusion, mandibular prognathism, limited extension of the elbow, muscle weakness, and arthralgia [5,7]. Some cases may present spinal deformities such as scoliosis [1,7].

Considering both the rarity of this disease and its typical radiographic presentation, we report the cases of two female siblings, daughters of consanguineous parents, with an emphasis on imaging findings. We also discuss the differential diagnosis along with a brief review of the literature.

Case report

Case 1

A 53-year-old woman was referred to the radiology department complaining of genu valgum and joint pain. Her family had noted widening of the knees at the age of 8 years, which progressed over time. There was no functional disability. The patient sought medical care several times, receiving the diagnosis of osteoarthritis with no further investigation. Over the last year, she had developed a more pronounced arthralgia that was not relieved by common analgesics. There was no visual, auditory, cognitive, or psychomotor disturbance.

The most evident finding on physical examination was the marked genu valgum (Fig. 1).

Mild facial dysmorphism, prognathism, and prominent ears and frontal bossing were also noted. The patient showed partial edentulism with caries and poor hygienic condition of the remaining teeth. There were no signs of anemia, jaundice, organomegaly, fractures, or motor disturbances.

Family history revealed parental consanguinity and similar phenotypic characteristics in 2 of her 8 siblings. The parents had no musculoskeletal deformities (Fig. 2).

Laboratory tests did not show any significant alterations.

Conventional radiography plain films of the patient's knees revealed Erlenmeyer flask deformity, characterized by marked femorotibial metaphyseal flaring, and associated cortical bone thinning (Fig. 3).

The additional radiographic survey, which included other long bones, skull, and spine, exposed the symmetry and the systemic nature of the skeletal disorder. Most of the long bones showed undertubulation and loss of their usual morphology. The proximal portions of the clavicles and ribs were expanded (Fig. 4A), as well as the proximal two-thirds of the humerus, which presented an arcuate shape (Fig. 4B). Other tubular bones shared similar characteristics, such as the distal portions of the radius and ulna, proximal and distal portions of the fibula, head of the metacarpals, and base of the phalanges (Fig. 4C). The ischiopubic rami were also diffusely enlarged, thereby narrowing the obturator foramina (Fig. 4D). Despite striking changes in tubular bones, skull radiographs showed only mild basal sclerosis, mandibular prominence, and poor pneumatization of paranasal sinuses and mastoid air cells (Figs. 4E and F).

Preoperative three-dimensional tomographic reconstruction of the lower limbs for surgical planning provided detailed analysis of the Erlenmeyer flask deformity and highlighted the S-shaped aspect of the tibia (Fig. 5A).

Additional T1-weighted magnetic resonance imaging (MRI) of knees revealed normal bone marrow signal intensity (Fig. 5B).

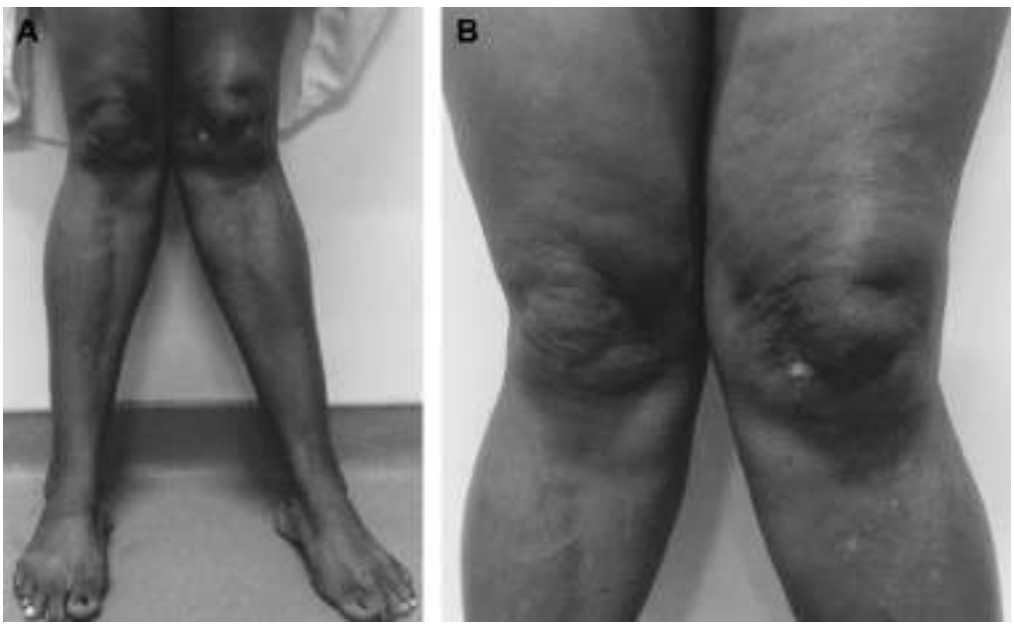

Fig. 1 – Photographs of the lower limbs of patient 1. (A) Genu valgum deformity. (B) Zoomed-in view. Greater detail of the bilateral widening of distal thighs and knees, accompanied by genu valgum.

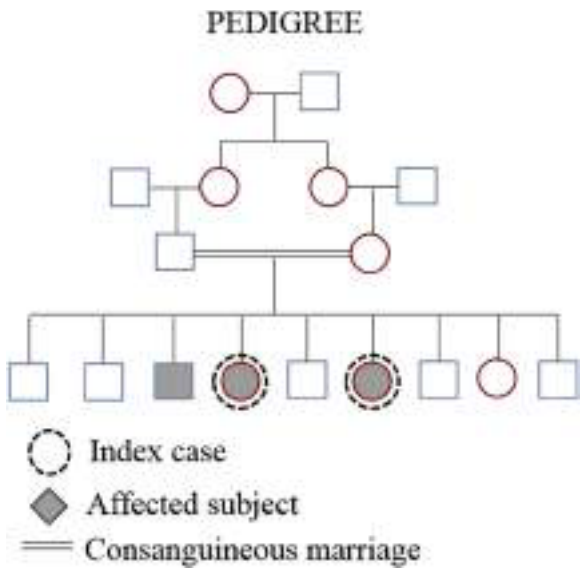

Fig. 2 – Pedigree. Parental consanguinity is demonstrated, and of the 9 offsprings, 3 are affected.

Case 2

A 46-year-old woman was referred to the radiology department after detection of bone changes in her sister (case 1). Her family noted genu valgum deformity at 5 years and dental changes at 10 years. From the third decade on, she complained of pain and proximal weakness of the lower limbs. Other symptoms included a bilateral limitation on shoulder abduction and elbow extension. There were no hearing, visual, or cognitive impairments.

Just like patient 1, the most notable finding on physical examination was the genu valgum (Fig. 6A). Patient 2 shared similar phenotypic characteristics, including mild facial dysmorphism, prognathism, prominent ears, and frontal bossing. The analysis of the dental arches demonstrated even more dramatic abnormality, with malocclusion, poor hygiene condition, tooth decay, and a high-arched palate (Fig. 6B). No hepatosplenomegaly or clinical signs of anemia, jaundice, or cranial nerve palsies were present.

Laboratory tests did not show any relevant information.

Conventional radiographic plain films showed essentially the same imaging findings of case 1. The knees exhibited Erlenmeyer flask deformity, and other tubular bones presented metaphyseal flaring to similar degrees and in the same locations. Mild cranial changes, S-shaped tibia, and expanded ischiopubic rami were also detected (Fig. 7).

Lumbar spine evaluation also showed no significant abnormalities (Fig. 8).

Because progressive worsening of arthralgia was refractory to treatment with analgesic drugs, the two reported patients remain under clinical follow-up at orthopedic clinics, whereas preoperative tests are being carried out, before surgical treatment can be performed. The third affected sibling is currently living in a different area of the country, and contact was not possible.

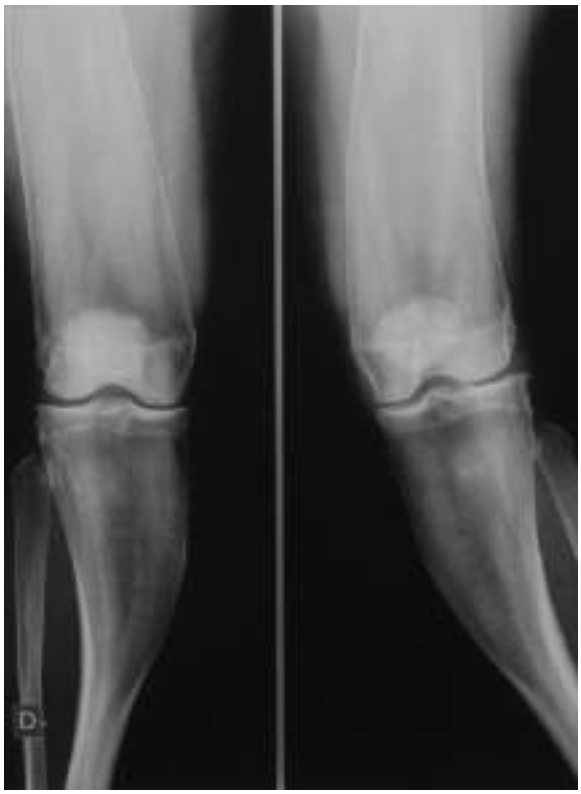

Fig. 3 – Knee radiographs of patient 1. Conventional knee radiographs in anteroposterior view showing Erlenmeyer flask deformity, characterized by femorotibial metaphyseal flaring, cortical bone thinning, and genu valgum.

Discussion

Pyle's metaphyseal dysplasia is a rare genetic disease with an estimated prevalence of less than one case per million. Until the 1980s, there were only 20 cases described in the literature, including countries like the USA, France, Germany, South Africa, India, and Italy [6], with fewer than 30 genuine cases reported to date [2]. The mutation involved is still unknown [1,2], with a lack of comprehensive genetic studies on the subject.

The pedigree evaluation of our patients leaves no doubt as to the autosomal recessive pattern of inheritance of this disorder: the patients' parents were first cousins, had a normal phenotype, and 30% of their offspring was affected. Both this pattern of inheritance and parental consanguinity are consistently reported in the literature worldwide [6]. Heterozygous individuals may have minimal skeletal changes [5].

The disease is characterized by defective metaphyseal remodeling that leads to massive metaphyseal widening of the long bones [1,6], with a significant reduction in cortical thickness and osteoporosis [5,6]. Pyle postulated a failure of bone resorption as the pathophysiological basis of the disease, which would lead to superposition of several layers of undermodeled bone at the metaphyseal segment [4].

Radiographic findings included marked metaphyseal expansion and cortical thinning of the long bones, associated with more pronounced radiolucency in affected areas [6]. Bone changes are most apparent in the proximal tibia and

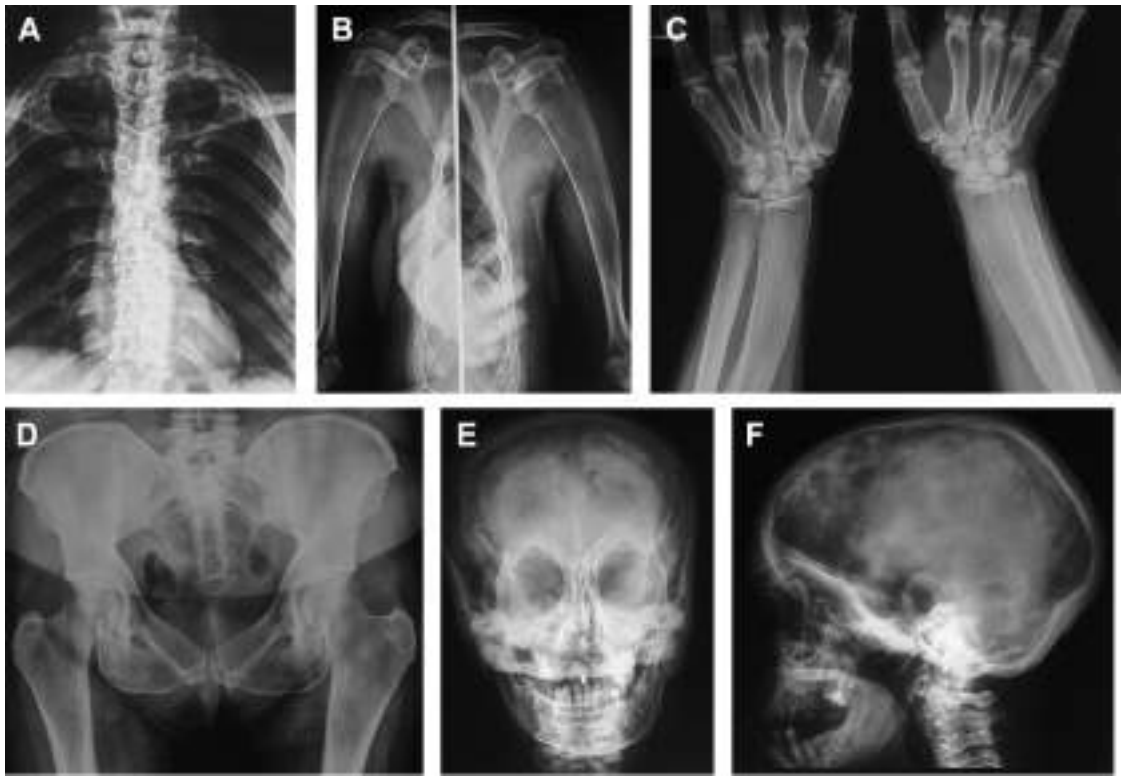

Fig. 4 – Conventional radiographs of the skull, pelvis, and appendicular skeleton of patient 1. (A) Proximal metaphyseal widening of the clavicles and ribs. (B) Proximal humeral metaphyseal expansion and bowing. (C) Undermodeling of the distal radius and ulna, as well as the proximal phalanges and distal metacarpal bones. (D) Expanded morphology of the ischiopubic rami and narrowed obturator foramina. (E) and (F) Skull radiographs in anteroposterior and lateral views showing mild basal sclerosis, mandibular prominence, and poor pneumatization of the paranasal sinuses and mastoid air cells.

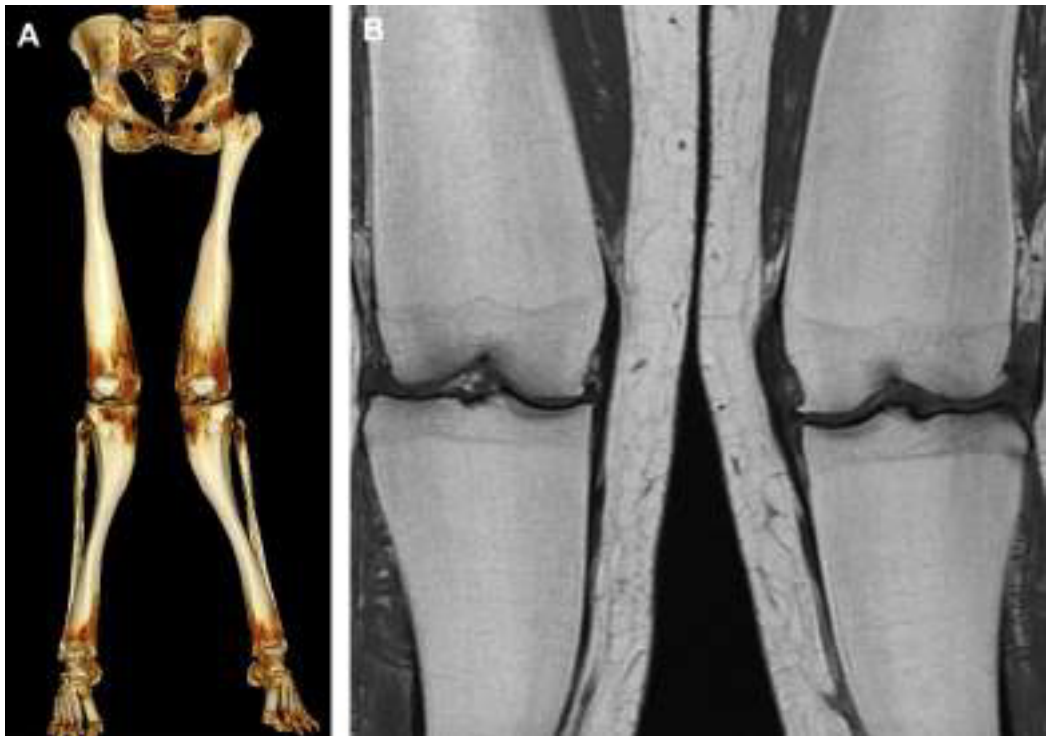

Fig. 5 – CT and MRI of the lower limbs of patient 1. (A) Three-dimensional tomographic reconstruction of the lower limbs and pelvis showing detail of the Erlenmeyer flask deformity, as well as the S-shaped aspect of the tibia. Note the narrowing of the obturator foramina secondary to the ischiopubic expansion. (B) T1-weighted coronal MRI of the knees showing bone undertubulation and signs of osteoarthritis, but an otherwise normal bone marrow signal intensity.

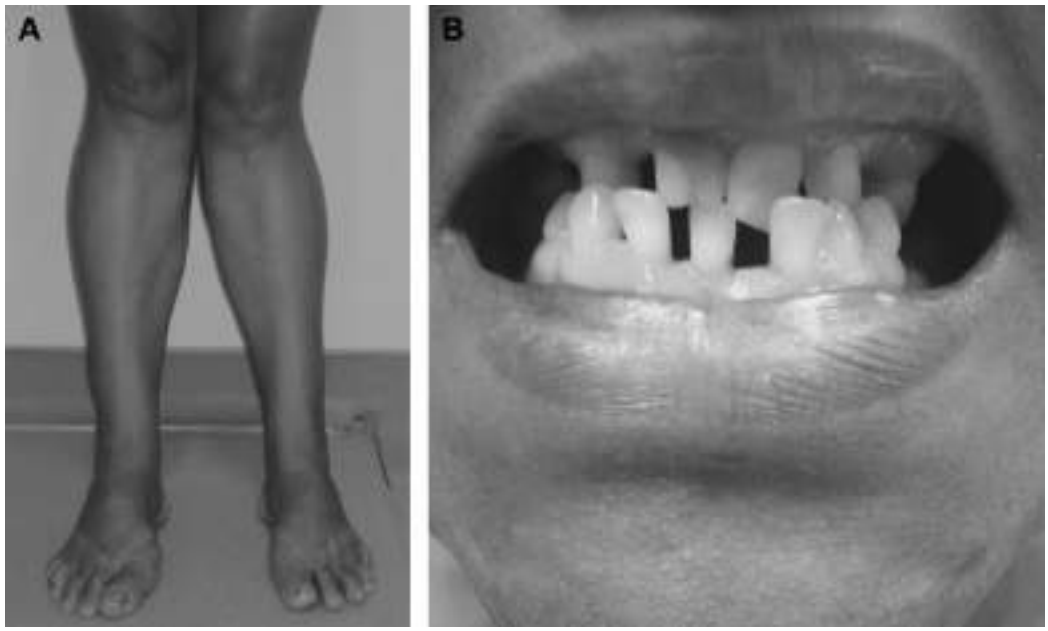

Fig. 6 – Photographs of the lower limbs and dental arches of patient 2. (A) Genu valgum deformity. (B) Prognathism, dental malocclusion, and poor hygienic condition.

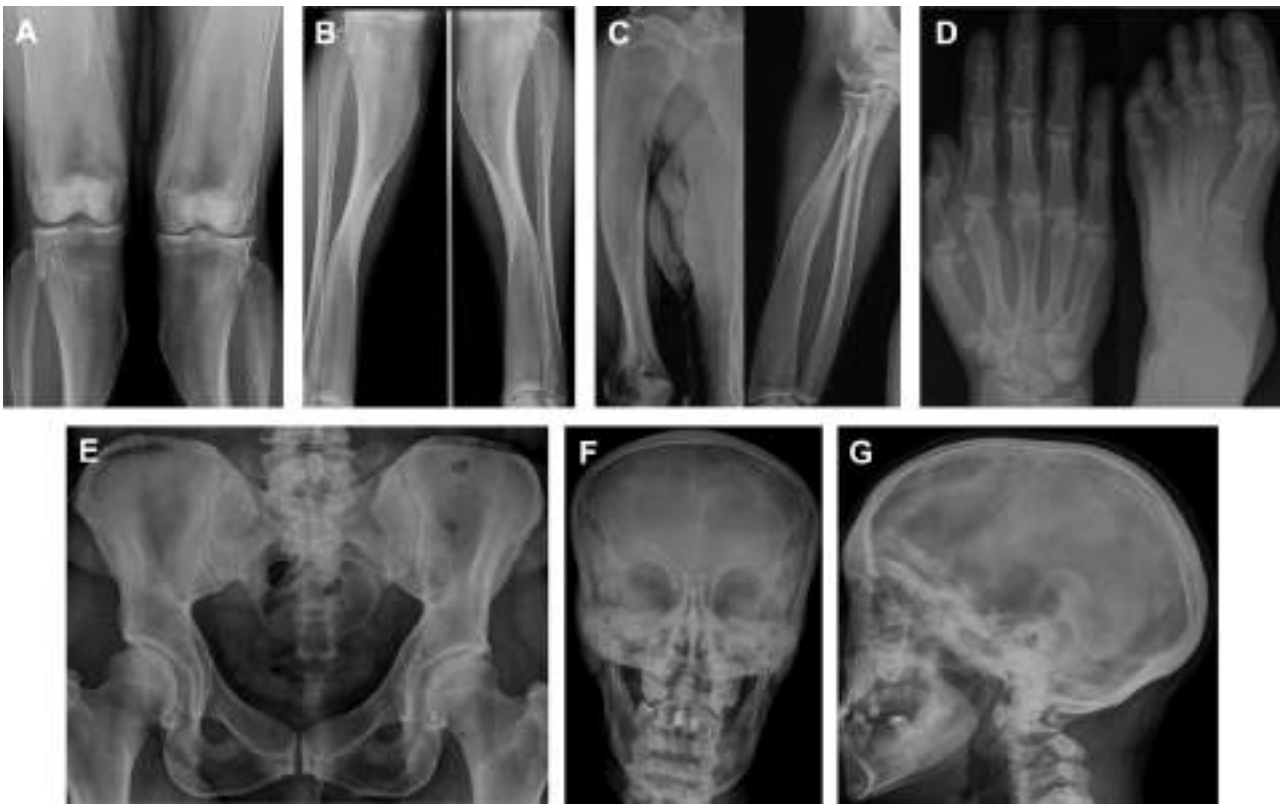

Fig. 7 – Conventional radiographs of the skull, pelvis, and appendicular skeleton of patient 2. (A) Erlenmeyer flask deformity. (B) S-shaped tibia. (C) and (D) Undertubulation of the long bones, including proximal humerus, distal radius, and ulna, proximal phalanges, distal metacarpal, and metatarsal bones. (E) Expanded aspect of the ischiopubic rami, narrowing of the obturator foramina. (F) and (G) Skull radiographs in anteroposterior and lateral views. There is mild sclerosis of the base and calvarium, frontal bossing, mandibular prominence, and poor pneumatization of the paranasal sinuses and mastoid air cells.

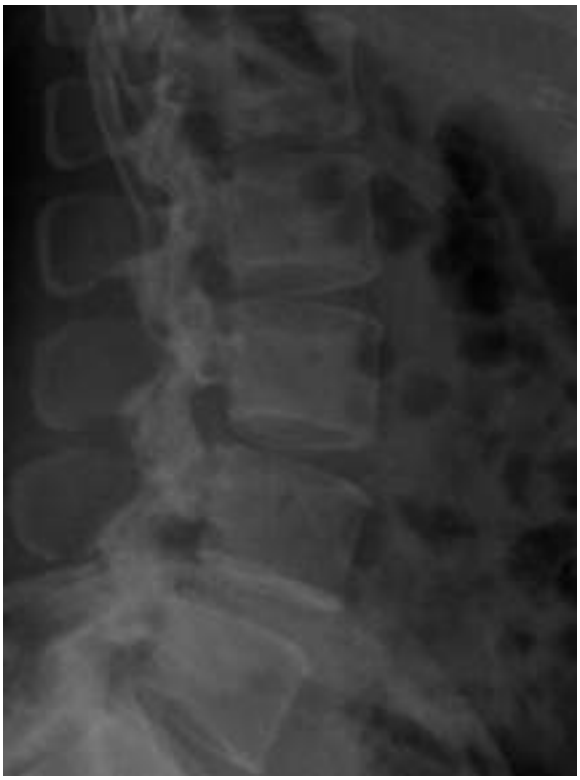

Fig. 8 – Lumbar spine radiograph of patient 2. Conventional radiograph of the lumbar spine in lateral view revealed no significant abnormalities.

distal femur, locations where the Erlenmeyer flask deformity is highlighted [1,8]. Radiographic spinal examination may reveal moderate platyspondyly and a biconcave lens shape of the vertebral bodies [5]. The skull analysis sometimes exhibits mild patchy basal and cranial vault sclerosis, as well as poor pneumatization or even obliteration of the paranasal sinuses [1,2]. In our patients, such imaging findings were all present, except for spinal changes.

The differential diagnosis of Erlenmeyer flask deformity-associated diseases includes craniotubular dysplasias, especially craniometaphyseal and craniodiaphyseal dysplasias, as well as Gaucher disease, osteopetrosis, thalassemia, and Niemann–Pick disease [5]. The absence of typical changes in laboratory tests and characteristic clinical manifestations rules out the possibility of storage disorders or hematologic conditions in our patients.

Often confused with Pyle's disease since its description, craniometaphyseal dysplasia is distinguished by its heterogeneous pattern of genetic inheritance, as well as its clinical and radiological findings. The autosomal recessive form of this craniotubular dysplasia has several differing characteristics from Pyle's disease, primarily by presenting more aggressively, with marked sclerosis and craniofacial hyperostosis, associated with symptoms such as progressive nasal obstruction, facial distortion, and especially multiple foraminal stenoses, leading to compression of the cranial nerves and consequent progressive mixed hearing loss, visual changes, and facial paralysis [8]. In 1970, Gorlin established imaging criteria to aid in the differential diagnosis with craniometaphyseal dysplasia, including more pronounced metaphyseal widening in Pyle's disease, as well as costoclavicular and ischiopubic rami involvement [7]. The presence of such imaging findings, together with the paucity of clinical signs and symptoms, is clearly observed in our patients, favoring the definitive diagnosis of familial metaphyseal dysplasia.

Most cases of the disease are asymptomatic and do not require intervention; however sometimes, genu valgum and fractures require orthopedic treatment [6,7], whereas dental abnormalities may require intervention. Temporary tibial asymmetric epiphysiodesis or bilateral osteotomies can correct the progressive genu valgum deformity by promoting transitory interruption of the growth cartilage development on the inner surface of the tibia and therefore allowing bone remodeling in the tibial metaphysis [5].

Finally, as demonstrated by the above reported cases, even in a rare genetic disease scenario and despite the advanced techniques available in medicine, conventional radiography remains a powerful diagnostic tool. When the radiologist evaluates such a common abnormality as genu valgum, an associated Erlenmeyer flask deformity may be the first clue to suspect Pyle's disease. Therefore, these cases highlight the pivotal role radiologists play in the correct diagnosis of this rare entity, allowing for appropriate genetic counseling, family support, and multidisciplinary treatment approach.

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