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CASE REPORT

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Familiar osteopoikilosis: Case report with differential diagnosis and review of the literature

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Abstract

Osteopoikilosis (OP) is a rare autosomal dominant sclerosing bone disease, caused by heterozygous mutations in the LEMD3 gene. It is characterised by numerous focal lamellar bone compact deposits in the spongiosa. In this case report, we describe a famliar case of OP and review the literature.

KEYWORDS

enostoses, LEMD3 gene, osteopoikilosis, sclerosing bone dysplasia

1 | INTRODUCTION

Sclerosing bone dysplasias (SBD) is a group of heterogeneous diseases that can cause an increase in generalized or segmented bone mass. They can be a primary disease that may or may not be hereditary or may, in fact, occur secondary to other diseases. SBDs are characterized by a disequilibrium between osteoblastogenesis and osteoclastogenesis, as we have previously described in another case.[1]

Osteopoikilosis (OP) is a rare autosomal-dominant sclerosing disease. It is characterized by numerous circular or ovoid sclerotic bone lesions symmetrically distributed in the epiphyses and metaphyses of the long bones and pelvis.[2,3] A loss-of-function mutation in the LEM domain-containing protein 3 gene (*LEMD3*) (OMIM *607844) has been related to OP. This gene encodes an internal nuclear membrane protein that interacts with both the BMP (bone morphogenic protein) and transforming growth factor beta (TGF-beta) signaling pathways, resulting in focal lamellar bone compact deposits in the spongiosa that have the appearance of an enostosis or "bone island".[4-6]

2 | CASE PRESENTATION

A 17-year-old boy was sent to our Regional Reference Centre for Bone Metabolic Diseases for the presence of multiple radio-opaque ovoid or circular lesions on an X-ray of the right

ankle (Figure 1). The young man was asymptomatic and had no history of fractures or other bone pathologies. He was not suffering from any other disease and did not take any medication. The subject's father was hypertensive; his mother and 20-year-old brother were in good health. The family history is otherwise irrelevant. The physical examination of the subject was normal, except for a mild squint, and there were no skin lesions. Clinical and laboratory tests, such as alkaline phosphatase, erythrocyte sedimentation rate (ESR), antinuclear antibodies (ANA), serum electrolytes, and tumor markers, were negative, except for mild hypovitaminosis D. On the suspicion of a systemic sclerosing bone disease, he was subjected to pelvis and hand X-rays which confirmed the presence of numerous enostoses (Figure 2), similar to those observed in the right ankle. In addition, the pelvis radiograph showed longitudinally oriented bands of confluent sclerotic lesions extending from the epiphyses and included the metaphyses. The X-ray pattern was suspect for OP; therefore, genetic counseling was provided. Molecular analysis of *LEMD3* identified the presence of a heterozygous germline mutation c.1754dup (Asn585Lysfs*15), which resulted in a frameshift within exon 5 of the gene and led to the subsequent generation of a premature stop codon 15 amino acids downstream from the mutation (Figure 3A). The father of the patient presented a similar radiological pattern (Figure 4), and molecular examination confirmed the same mutation as that present in the son (Figure 3B). Figure 5 shows the genealogical tree of the patient's family; the other family members were not subjected to molecular investigation. The mutation c.1754dup has not been reported in mutational databases such as LOVD (Leiden Open Variation Database) or Clinvar and, according to the type of genetic alteration and the segregation with the disease in the family, it is a pathological mutation. The two subjects (father and son) are part of a case series of 27 patients, recently published,[7] representing the largest up-to-date Italian study describing clinical and radiological findings with a LEMD3 molecular characterization.

3 | DISCUSSION

Osteopoikilosis (osteopathia condensans disseminata, or "spotted bone disease") is an asymptomatic disease first described by Albers-Schönberg in 1915.[2] It is characterized by an abnormality in bone maturation during endochondral ossification, with the formation of circular or oval sclerotic lesions of 2-10 mm in size which are symmetrically distributed in the epiphyses and metaphyses of the long bones and pelvis. It appears during childhood and persists throughout life. The male to female ratio of this disease is 3:2.[3] OP is an inherited autosomal-dominant disorder caused by a loss-of-function mutation in the LEMD3 gene. A simple X-ray is usually enough to make a diagnosis of OP. Magnetic resonance imaging (MRI) can help in differential diagnosis of more complicated cases, but there are few reports in the literature.[8,9] A bone scan can also help to distinguish from osteoblastic bone metastases, as OP lesions show a general absence of tracer uptake, although in the literature there are some reported cases of OP with an abnormal bone scan.[10,11] Moreover, in contrast to bone metastasis, the sclerotic lesions in OP are symmetrical, uniform in size and do not induce cortical erosion.

Osteopoikilosis must be differentially diagnosed from osteoblastic metastases, or from other sclerotic bone disorders such as melorheostosis, mastocytosis, osteopathia striata, Ollier's disease, tuberous sclerosis, and Paget's bone disease.[3,12,13]

In most cases OP is asymptomatic, but in 15%-20% of cases it presents with pain and joint effusion,[12] without

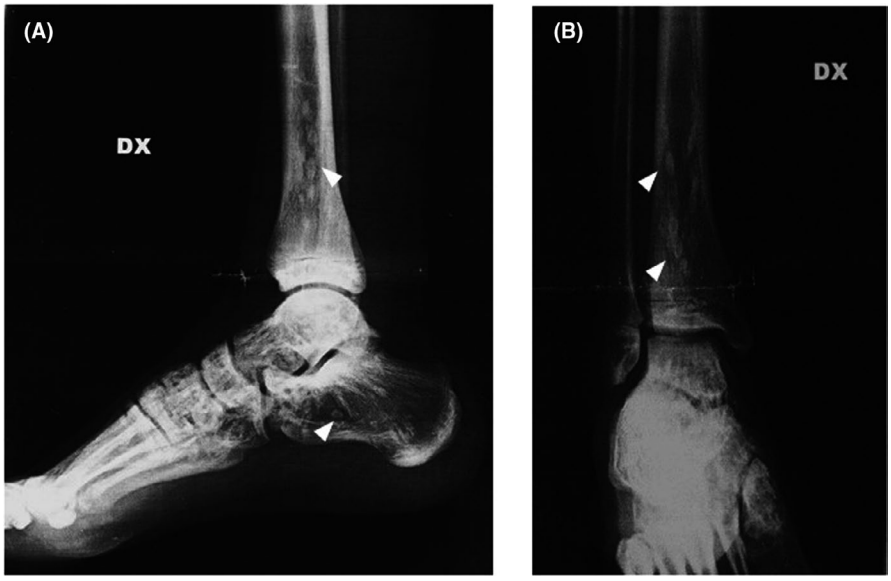

FIGURE 1 X-ray of the patient's right ankle (A, lateral view, B, anteroposterior view). Arrows indicate enostoses

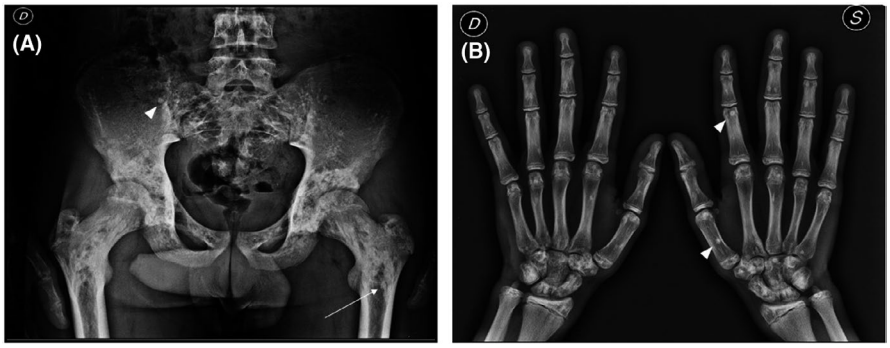

FIGURE 2 X-ray of the patient's pelvis (A) and both hands (B). Arrows indicate enostoses. Narrow arrow indicates confluent sclerotic lesions

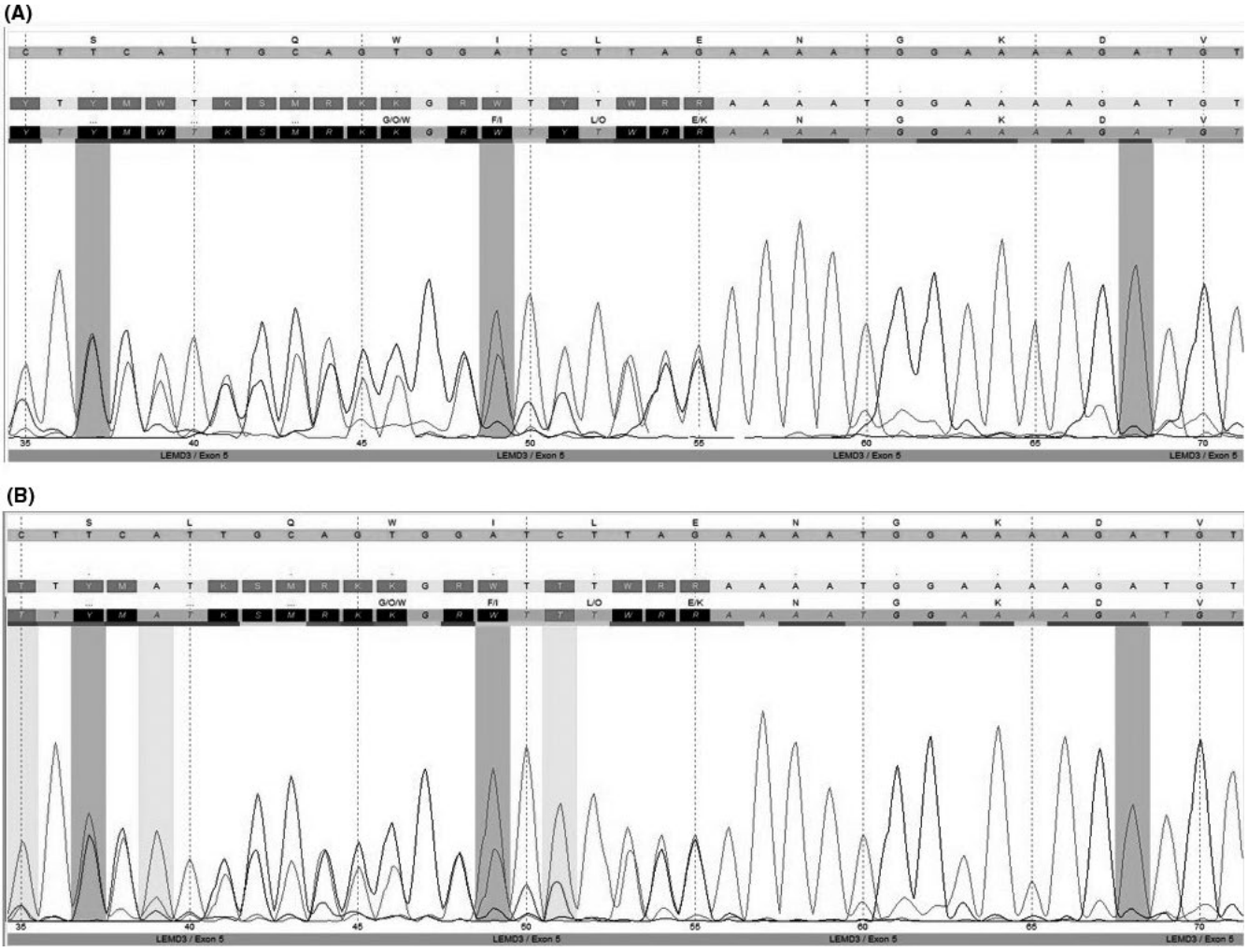

FIGURE 3 Electropherograms showing c.1754dup mutation in LEMD3 (A, reverse strand in the patient; B, reverse strand in the patient's father)

deformity or dysfunction at the local site. The origin of this joint pain is unknown. OP is sometimes associated with diffuse white skin lesions (dermatofibrosis lenticularis), similar to those observed in Buschke-Ollendorff syndrome.[14] OP can also be associated with other diseases such as melorheostosis, the tendency to keloid formation, spinal stenosis, dwarfism, tuberous sclerosis, and scleroderma.[3,15,16] In general, OP does not require any medical or surgical therapy.

In our case, as frequently reported in the literature data, the diagnosis of OP was made incidentally during X-rays performed for another indication. Confirmation of the clinical-radiological diagnosis by molecular analysis of the *LEMD3* gene allowed us to avoid further, unnecessary investigations and to acquire a differential diagnosis from other malignant diseases. Moreover, because OP is a genetic disease, information about inheritance and recurrence risk in other members of the family was offered.

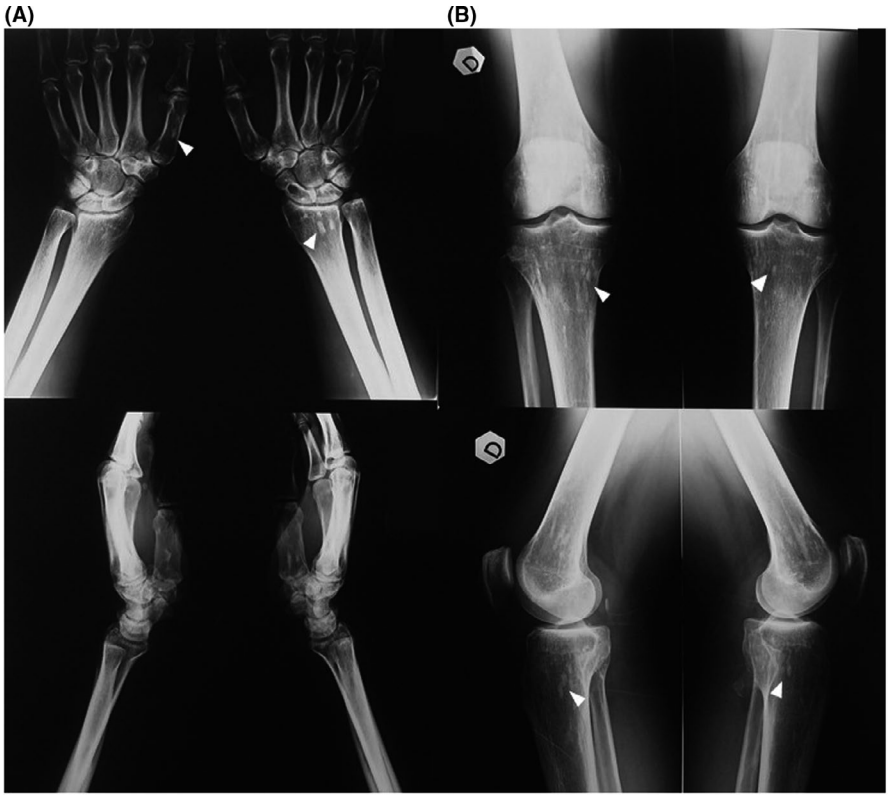

FIGURE 4 X-ray of both hands (A) and knees (B) of patient's father. Arrows indicate enostoses

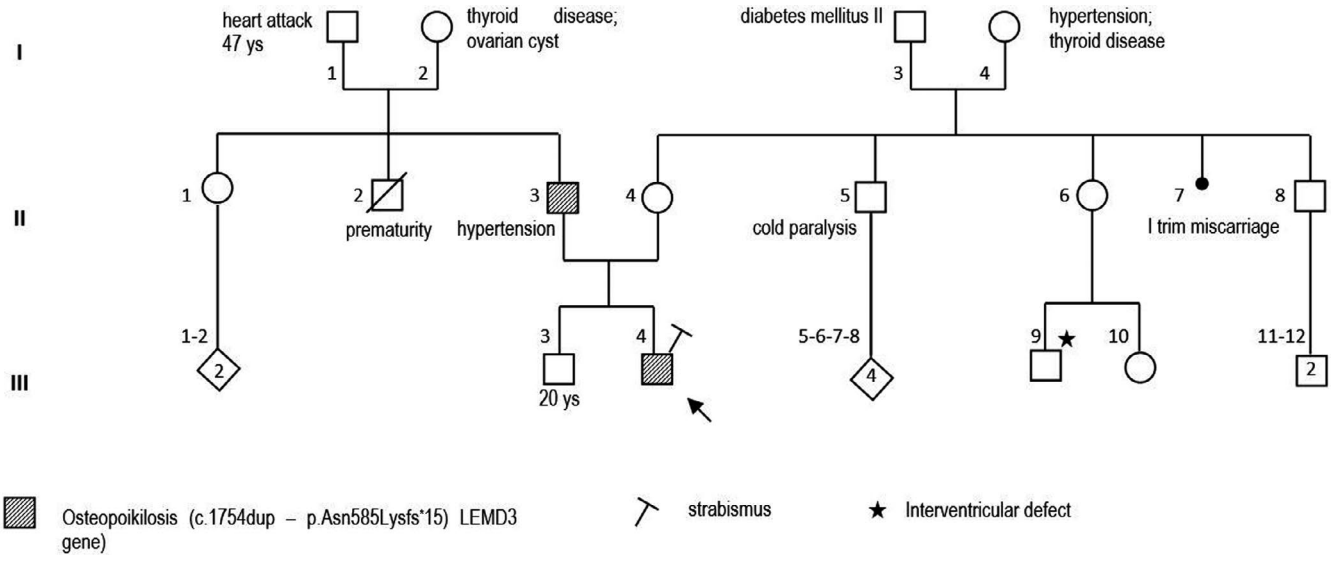

FIGURE 5 Genealogical tree of the patient's family

In conclusion, OP is a benign and asymptomatic disease whose diagnosis usually occurs accidentally. A precocious and correct diagnosis is important to exclude a malign disease and avoid useless examinations.

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CONFLICT OF INTEREST

The authors declare no conflict of interest regarding this publication.

AUTHOR CONTRIBUTIONS

AG and PC: wrote the initial draft of the manuscript. MG, EP, and LS: performed the molecular analysis of LEMD3 gene. AX, CG, and TM: assisted in the preparation of the manuscript. RR, AC, and LZ: performed the literature

research. All authors reviewed and approved the final manuscript.

ETHICAL APPROVAL

Informed consent was obtained from the patient's parents for the publication of this case report.

DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this published article.

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