

Buschke–Ollendorff syndrome in a 6-year old patient: clinical and histopathological aspects of a rare disease

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Abstract

Buschke–Ollendorff syndrome (BOS) is a rare genetic hereditary genodermatosis characterized by benign skeletal and cutaneous lesions. Skeletal alterations known as osteopoikilosis (OPK) or “spotted bone disease” are asymptomatic areas of sclerosing dysplasia. Two skin lesion patterns have been described because they may be of either elastic tissue (juvenile elastoma) or collagenous composition (*dermatofibrosis lenticularis disseminata*). We present the case of a 6-year-old male patient with yellowish papules that coalesced to form plaques localized on both thighs and on the upper limbs consistent with a connective tissue nevus (CTN) diagnosis. X-ray examination of the skeletal system revealed the presence of multiple small areas (measuring between 1 and 7 mm) of increased bone density (OPK) bilaterally. A skin biopsy was performed and did not show striking alterations in the number or dimension of the extracellular matrix fibers, but it showed mucin deposition between them, which is compatible with a CTN. This study reports on the clinical presentation and histological examination of this unusual disease.

Keywords: Buschke–Ollendorff, connective tissue nevi, pediatric, osteopoikilosis

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Introduction

Buschke–Ollendorff syndrome (BOS) is a rare genetic hereditary genodermatosis. With an estimated incidence of 1:20,000, it was described for the first time in 1928, when Abraham Buschke and Helene Ollendorff Curth defined the syndrome in a 45-year-old female patient as *dermatofibrosis lenticularis disseminata* (1).

BOS is characterized by cutaneous and skeletal abnormalities. Skin lesions are multiple elastic hamartomas and they have two main histological patterns: elastic tissue and collagenous fibers, also known as juvenile elastoma and *dermatofibrosis lenticularis disseminata*, respectively (2). Osteopoikilosis (OPK) causes skeletal lesions that can be detected by radiographic imaging. They are characterized by increased bone density of the cancellous bone, involving the proximal and distal extremities of the long bones of the limbs and hands, and the pelvis (3).

Case report

We report the case of a 6-year-old boy that visited our dermatological unit and presented with yellowish papules coalescing to form plaques localized on both thighs and the upper arms (Fig. 1). These papulonodular lesions first appeared a few months after birth without any other related symptoms. The child's growth was regular and his general health was good. He was not referred in the past for bone fractures or episodes of bone swelling.

Physical examination revealed the presence of several normochromic oval papules and plaques, some of which were slightly yellowish, with various shapes and sizes, ranging from 1 to 5 cm in diameter, distributed on both thighs and the upper arms (Fig. 1). Systemic examination was otherwise unremarkable.

One of the left thigh lesions was biopsied. Histological findings

showed a normal epidermis at the hematoxylin and eosin (H&E) sections, whereas the spaces between the collagen fibers in the dermis were slightly increased (Fig. 2a), with a positive Alcian blue stain for mucine (Fig. 2b). No findings of thickening or increase in elastic fibers were detected by the Verhoeff–Van Gieson stain.

A total body X-ray examination was performed to study the skeletal system, and it revealed the presence of multiple small areas (measuring between 1 and 7 mm) of increased bone density (OPK) bilaterally; in particular, they were located in the lateral angle of the scapula near the glenoid fossa, in the pelvic bones, and in the proximal and distal epiphyses of the tibia and fibula,



Figure 1 | Slightly yellowish and normochromic plaques on both thighs.

femur, radius and ulna, and humerus (with some areolas also in the middle of the shaft of the right distal humerus; Fig. 3). Both the boy's mother and his grandmother denied the presence of similar skin lesions, but after seeing the child's radiological lesions they claimed to have similar bone changes.

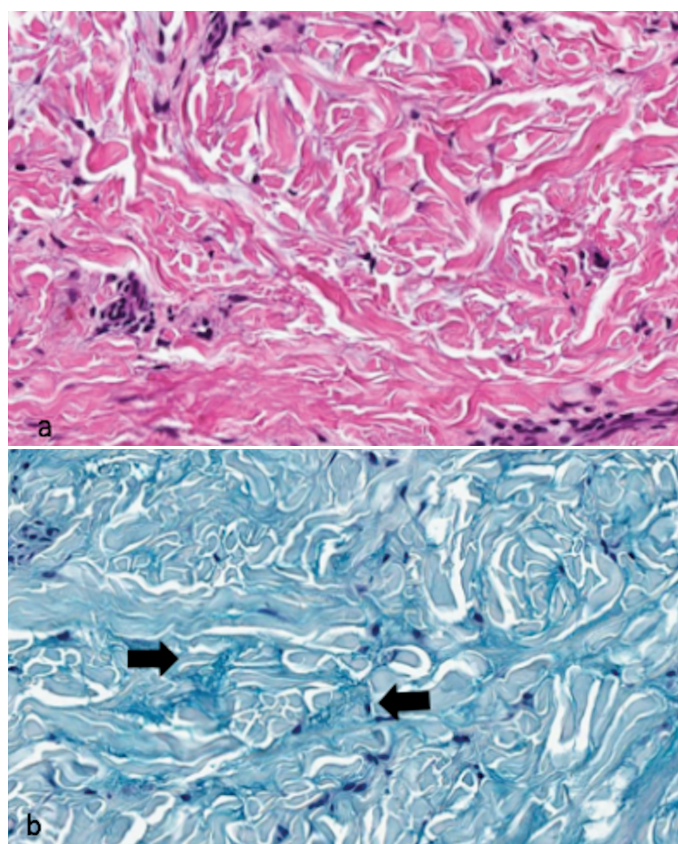


Figure 2 | a) Increased spaces between collagen fibers in the dermis (400 × H&E); b) evidence of mucin.

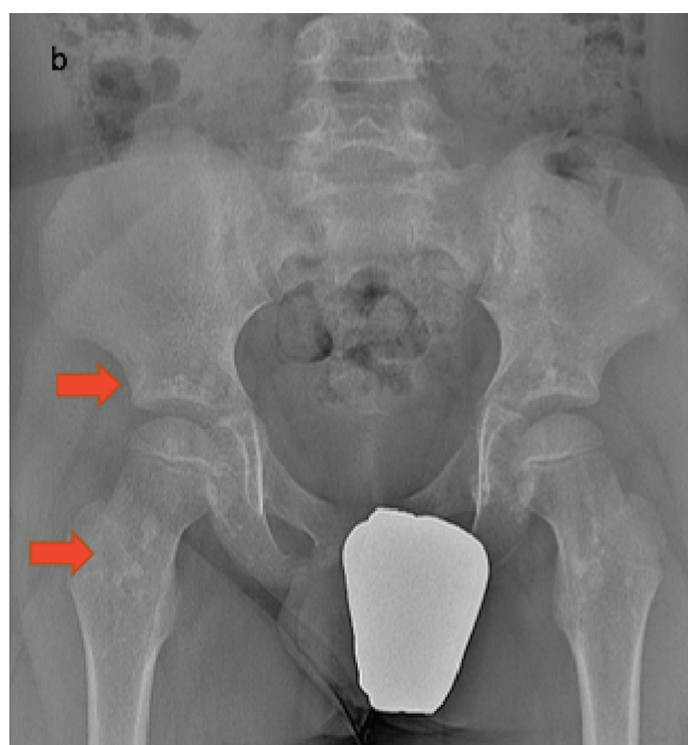
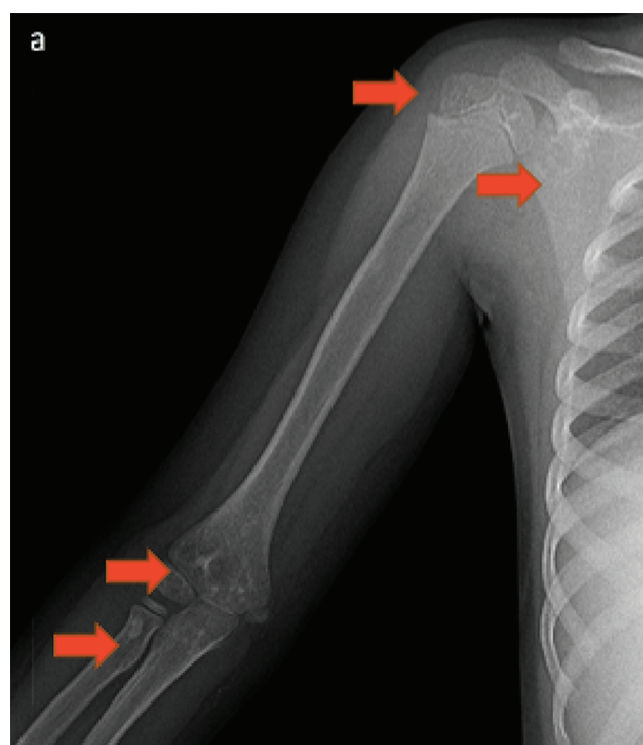


Figure 3 | Radiologically dense opacities seen in the scapula, humerus, radius, pelvic bones, and femur.

Discussion

BOS is a benign hereditary genodermatosis with an estimated incidence of 1:20,000 (2), which results from mutations of the LEM domain-containing protein 3 (LEMD3) gene (12q14.3), also called MAN1, with an autosomal dominant trait, incomplete penetrance, and no sex or racial predilection (3, 4). The name LEMD3 stands for 'LEM domain-containing protein 3', and protein 3 is an integral protein of the inner nuclear membrane of the nuclear envelope that antagonizes both the transforming growth factor-beta (TGF- β) and the bone morphogenic protein (BMP) pathways (5). As happens in BOS, loss-of-function mutations in this gene reducing the amount of functional protein are associated with increased signaling through these two pathways, which are implicated in many cellular functions and in the growth of connective tissue. Investigations conducted in cultured fibroblasts of patients affected by BOS show that in the presence of calf serum production of tropoelastin increases from two to eight times above normal (6). In support of this, the skin of individuals with BOS has revealed elevated elastin mRNA levels, which are linked with increased production of this protein in the extracellular matrix (6). Hence, the enhanced signaling of these cellular pathways could explain the characteristic skeletal and cutaneous lesions of the syndrome. Bone alterations and connective tissue nevi (CTNs) are usually both present in patients affected by BOS, but several subjects have presented only skin or skeletal lesions. Due to the variable expressivity of the disease, various phenotypes are possible in the same family (7). Skeletal alterations known as OPK or "spotted bone disease" are asymptomatic areas of sclerosing dysplasia. At the X-ray examination multiple increased bone density areas can be detected in the spongiosa of metaphysis and epiphysis of long bones, the pelvis, feet, and hands. It is often diagnosed as an incidental finding on radiographs obtained for another purpose, and it should not be confused with metastatic osteoblastic lesions.

Contrary to OPK, osteoblastic metastases are usually asymmetric, vary in size, and tend to affect the axial skeleton with osseous destruction and periosteal reaction (8). Alkaline phosphatase level, scintigraphy, and bone biopsy could be carried out for additional confirmation. OPK will not show increased alkaline phosphatase for the age, radiotracer uptake, or positive tumor markers at immunohistochemistry (9). Another skeletal disorder that can be associated with BOS, even more rarely, is melorheostosis. This is another sclerosing mesenchymal dysplasia that can be either monostotic or polyostotic, usually unilateral and monomelic, in which the bony cortex widens and become hyperdense in a sclerotomal distribution. The thickening of the bony cortex appears in the radiographs with the characteristic aspect of “dripping wax candle” (2). Unlike OPK, melorheostosis is often symptomatic and associated with pain, joint contractures, and deformity of the affected limb (4). Frequently features of melorheostosis and OPK may coexist in overlap syndromes that share loss of function mutations in the *LEMD3* gene in their etiology. Regarding the dermatological manifestation, CTNs are circumscribed hamartomas of the dermal extracellular matrix of the elastic type, collagenous composition, and/or proteoglycans. They can be solitary or multiple, acquired or congenital, and sporadic or possibly associated with syndromic disorders, which should prompt various differential diagnoses (10). They usually consist of multiple firm papules or nodules that coalesce into plaques, normochromic or yellowish, which give an irregular appearance to the skin surface. These lesions are usually present at birth or appear in the first years of life, rarely in adulthood, and tend to be located on the trunk, proximal extremities, and skin folds. CTNs can enlarge with the growth of the child but remain asymptomatic (11). Other rare manifestations reported in BOS are otosclerosis with hearing impairment, congenital spinal stenosis, short stature, aortic stenosis, and diabetes mellitus (12–14). The rarity of the syndrome and the few cases reported in literature do not make it possible

to establish whether there is a statistically significant association with these conditions. However, BOS generally follows a benign course, and cutaneous and bone lesions are usually asymptomatic and often found as incidental findings (15). From a histological point of view, collagenomas, which tend to be rarer than elastomas in BOS, show a thickened reticular dermis with haphazardly arranged thickened collagen bundles. The increased amount of collagen fibers, with either normal or decreased elastic tissue, can be demonstrated with special stains such as Masson’s trichrome for collagen and Verhoeff–Van Gieson for elastic fibers. Elastoma’s histopathological examination usually shows increased spaces between elastic fibers in the dermis, which can be increased in number and thickness, and coarsely braided. However, the histological features of CTNs are very variable and may change between individuals of the same family or even between different lesions of the same patient (10). The histology of our case was singular because it did not show striking alterations in the number or dimension of the extracellular matrix fibers, but a mucin deposition between them, which is compatible with a CTN and has also been described in another case report of BOS (16).

Conclusions

The goal of this case report was to communicate that an overall analysis of clinical manifestations, familiar medical history, radiographic findings, and histology allowed us to make a diagnosis of BOS without carrying out any genetic testing to avoid further expensive exams. Thus, as demonstrated in this case report, a diagnosis of BOS must result from collaboration between a dermatologist, pathohistologist, and radiologist. In conclusion, diagnosis of the syndrome is not simple, but it is very important to reassure patients and family members as well as to avoid unnecessary examinations and follow-up investigations.

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