Buschke-Ollendorff Syndrome: Sparing Unnecessary Investigations

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Practice Points

- Buschke-Ollendorff syndrome (BOS) is an autosomal-dominant disease characterized by the rare association of skin lesions consisting of collagen or elastic nevi and bone lesions known as osteopoikilosis that are reported radiologically.
- Buschke-Ollendorff syndrome is characterized by elevated genetic heterogeneity and is transmitted with a variable expression.
- Although BOS is a benign condition and does not require any treatment, a correct diagnosis is important to spare patients from unnecessary investigations.

Buschke-Ollendorff syndrome (BOS) is an autosomal-dominant disease characterized by the association of connective tissue nevi and osteopoikilosis. It is diagnosed by mutations of proteins involved in bone and connective tissue morphogenesis. We report 2 cases of BOS with different cutaneous clinical patterns. These cases emphasize the importance of heightened suspicion of BOS in selected cases. Identifying BOS can be reassuring for the patient, sparing futile and expensive investigations.

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Buschke-Ollendorff syndrome (BOS) is a rare disease that is inherited in an autosomal-dominant fashion with high penetrance. It is characterized by osteopoikilosis associated with skin manifestations. The approximate incidence of the disease is 1:20,000, with few cases reported in the literature since 1928.[1] Skeletal lesions known as osteopoikilosis are areas of increased bone density that can be seen on radiographic imaging and typically are located in the substantia spongiosa of the epiphyses and metaphyses of long bones and the pelvis. In BOS, cutaneous lesions consist of elastic or collagen nevi. Phenotypic expression of the disease is variable, and skeletal and cutaneous lesions may occur separately. Gene mutations of proteins involved in bone and connective tissue morphogenesis have been described in patients with BOS.[2-5]

Case Reports

Patient 1—A 17-year-old adolescent girl was referred to our hospital for evaluation of an incidental finding of osteopoikilosis that had been noted in the setting of a traumatic event. Clinical examination revealed cutaneous lesions characterized by asymptomatic, linear, stringlike and atrophic fibrotic plaques localized symmetrically on the trunk, right buttock, and right thigh (Figure 1). The lesions on the thigh were present at birth and had spread progressively to the other areas. There was no known history of inflammatory skin disease to explain the presence of the lesions, and no family history of similar signs or symptoms was reported. Histopathologic examination of a punch biopsy of a plaque from the trunk revealed increased collagen bundles associated with thick interlacing elastic fibers. The epidermis

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did not show any specific histologic alterations. These histopathologic features were diagnostic of a connective tissue nevus (Figure 2).

Radiographic imaging of the hands and feet revealed numerous small, ovoid or round foci of sclerosis that were a few millimeters in diameter and were occasionally confluent. This finding was prevalent on the carpal and tarsal bones but less evident on the phalanges and the epiphysis of the metatarsal and metacarpal bones. Full radiographic imaging of both arms and legs subsequently was obtained and showed similar lesions predominantly in the substantia spongiosa of the metaphyses and the epiphyses of the humerus, femur, tibia, and fibula bilaterally (Figure 3). Evaluation of the patient's parents revealed that her mother had sporadic lenticular areas of increased bone density seen on radiography of the carpal and tarsal bones, particularly at the level of calcaneus, and the proximal and distal humeral epiphyses.

These lesions in our patient were consistent with an incomplete form of osteopoikilosis, which reflects the known variable expression of BOS. The radiologic findings in addition to the cutaneous lesions and the positive family history supported a diagnosis of BOS.

Patient 2—A 5-year-old boy presented with multiple congenital, asymptomatic, flesh-colored papules with elastic consistency on the left thigh, back, and pubic area that were characteristic of dermatofibrosis lenticularis disseminata (Figure 4). The patient's 7-year-old sister had similar cutaneous lesions. The patient underwent a skin biopsy from the back that revealed thickening of collagen bundles in the dermis with an increase in elastic fibers (Figure 5). On

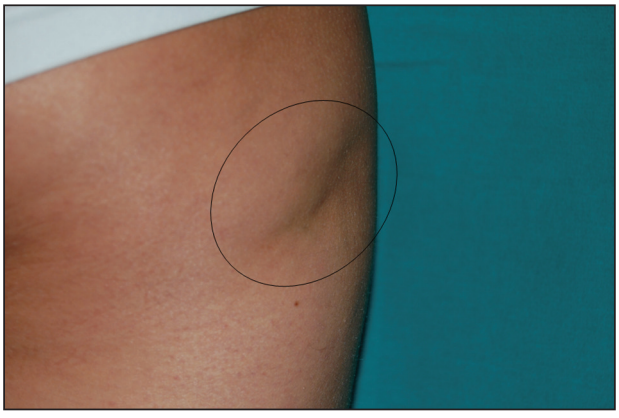

Figure 1. An asymptomatic atrophic fibrotic plaque localized on the right thigh.

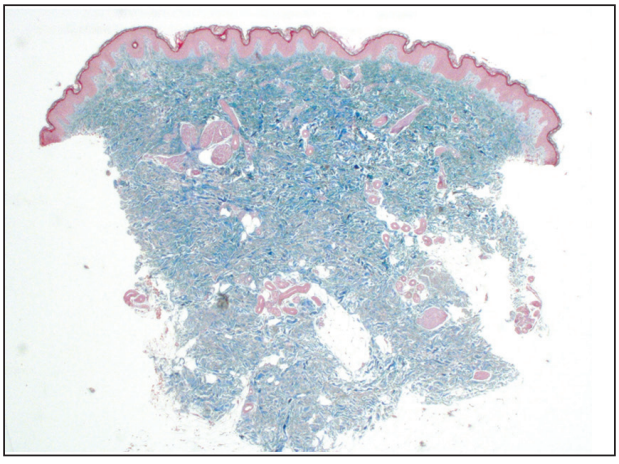

Figure 2. Low-power view of a punch biopsy showing a normal epidermis. Collagen bundles of the dermis were thickened and somewhat homogenized, as highlighted by the Masson stain (original magnification ×2.5).

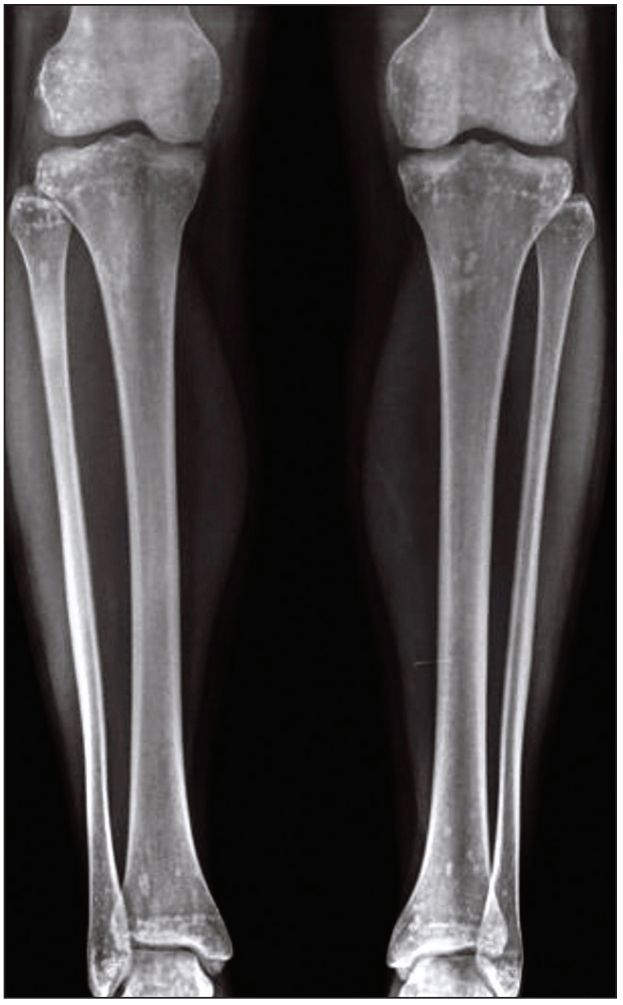

Figure 3. Radiograph of the legs revealed numerous small, ovoid or round foci of sclerosis on the substantia spongiosa of the metaphyses and the epiphyses of the femur, tibia, and fibula on both sides of the body.

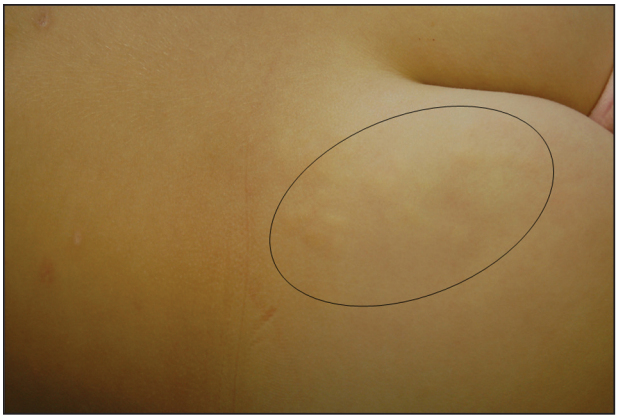

Figure 4. Multiple asymptomatic flesh-colored papules with elastic consistency on the back that were characteristic of dermatofibrosis lenticularis disseminata.

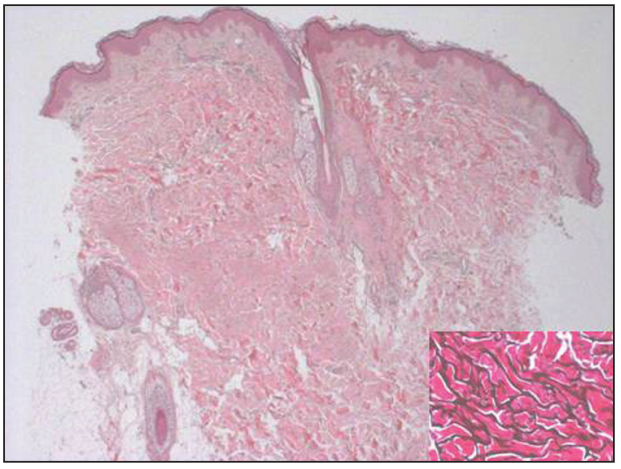

Figure 5. The epidermis and dermis appeared normal on histopathology; however, the elastic fibers were markedly increased in both size and number up to the deep dermis in the absence of degenerating changes (H&E, original magnification ×2.5; vascular endothelial growth factor, original magnification ×20 [inset in bottom right corner]).

radiographic imaging, small sporadic areas of sclerosis were noted in the substantia spongiosa of the lateral aspect of the humeral capitulum, the radial neck, the capitate, the head of the proximal phalanx of the fourth finger on the left hand, and the heads of the third and fifth middle phalanges on the left hand (Figure 6). Radiography revealed osteopoikilosis on both humeral heads in the patient's mother. These findings in addition to the dermatologic and histopathologic features suggested a diagnosis of BOS.

Comment

In 1928, Buschke and Ollendorff[1] first reported the association between osteopoikilosis and dermatofibrosis lenticularis disseminata, which showed autosomal-dominant inheritance. Skin and bone lesions can occur independently in different family members. Two different clinical cutaneous patterns are described in BOS.[2-4] The first and most frequent form is characterized by yellowish nodules often grouped in plaques that are asymmetrically distributed, such as those seen in patient 1. The second form is known as dermatofibrosis lenticularis disseminata, which was seen in patient 2. Histologically, most lesions show normal collagen fibrils and an increased number of elastic fibers.

Osteopoikilosis, also known as spotted bone disease or osteopathia condensans, is a rare asymptomatic bone dysplasia of unknown etiology. It is characterized by an abnormality in the bone maturation process and often is found incidentally on radiologic examination, as seen in patient 1. Radiologic signs of osteopoikilosis consist of small, disseminated, well-circumscribed areas of increased radiodensity located in the epiphyses and metaphyses of long bones, as well as the pelvis, hands, and feet. These lesions, which typically are asymptomatic, could sometimes be associated with bone and/or joint pain but do not cause a predisposition to fractures. Documentation of these bone lesions by early adult life is important to avoid confusion with osteoblastic metastases on the skeleton.[6]

Buschke-Ollendorff syndrome is characterized by a variable expression. Loss-of-function mutations of the *LEMD3* gene have been described in association with this disorder.[7] This gene encodes an inner nuclear protein membrane with a C-terminal domain that binds SMAD2 and SMAD3 and antagonizes the bone morphogenetic proteins and transforming growth factor β. These proteins are involved in connective tissue morphogenesis, inducing elastin production from fibroblasts.[7] Seven novel loss-of-function mutations of *LEMD3* have been identified.[8] The segmental manifestation of BOS could be a consequence of the mosaicism resulting from a somatic mutation.[9,10] A case describing the absence of *LEMD3* mutation in an affected family suggested the genetic heterogeneity of BOS.[11]

Conclusion

Buschke-Ollendorff syndrome is a benign condition with no repercussions on the patient's health or quality of life. It does not require any specific treatment because the lesions generally remain asymptomatic and do not generate any substantial cosmetic burden. Mutation analysis was not performed in our patients because BOS has a

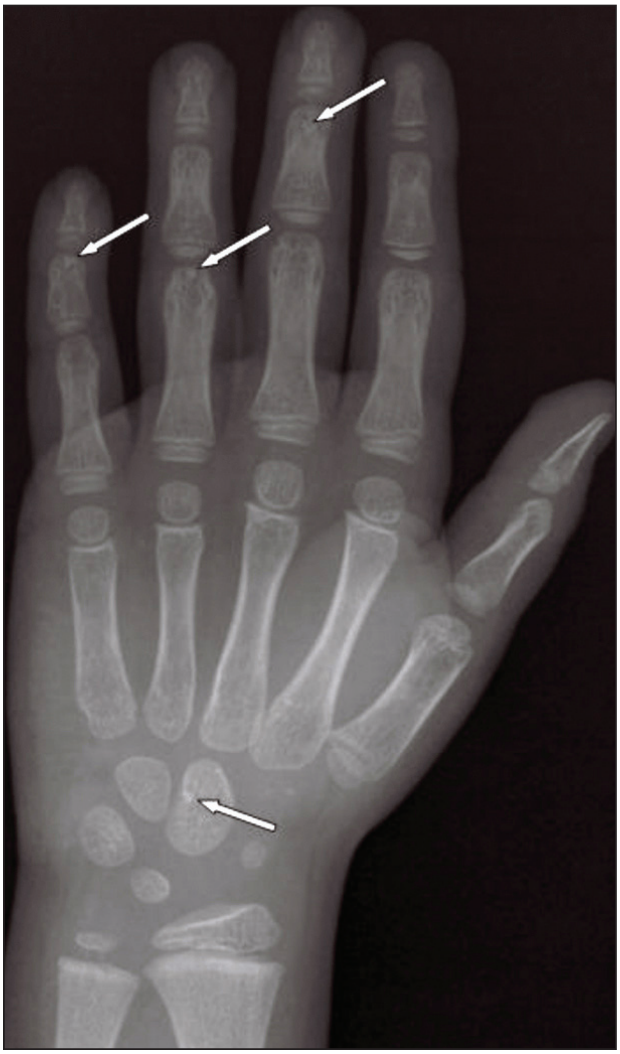

Figure 6. A radiograph of the left hand revealed small sporadic areas of sclerosis in the substantia spongiosa on the heads of some phalanges (white arrows).

good prognosis and the parents refused further investigation in both patients; therefore, a correct diagnosis was essential in our cases to rule out malignant bone disease in patient 1 whose osteopoikilosis prompted the workup and other disorders (eg, tuberous sclerosis, pseudoxanthoma elasticum) in patient 2 whose cutaneous lesions were the primary cause for presentation. A correct diagnosis of BOS is necessary to spare patients from expensive investigations and to provide reassurance about the benign nature of the disease.

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