



## Connective tissue nevi

Connective tissue nevi are hamartomas in which one or several components of the dermis is altered. Lesions in which collagen predominates are called collagenomas; lesions in which elastin predominates are called elastomas. A nevus mucinosis is a lesion in which an alteration in the amount of dermal glycosaminoglycan is present. The name nevus mucinosis is also used for lesions in which an alteration in more than one dermal component is present.

Connective tissue nevi may be solitary or multiple, sporadic or inherited. They may occur as isolated skin lesions, or they may be associated with a number of syndromes. One report described a collagenoma that occurred on the bulbar conjunctiva.<sup>1</sup>

Zosteriform connective tissue nevus is considered to be a separate entity because of its distribution and histopathologic characteristics.

The cause of connective tissue nevi is unknown. However, note that osteopoikilosis with or without the skin manifestations of Buschke-Ollendorf syndrome and with or without melorheostosis can be caused by heterozygosity for loss-of-function mutations in *LEMD3*,<sup>2</sup> also called *MAN1*, which encodes an inner nuclear membrane protein.

- Collagenomas and elastomas generally present during the postpubertal period.
- In Buschke-Ollendorf syndrome, the skin changes may be delayed until adulthood.
- Nevus mucinosis may present at birth, during childhood, or in adolescence

Collagenomas have been associated with multiple medical syndromes. For example, 72% of patients seen at the National Institutes of Health (NIH) for evaluation of multiple endocrine neoplasia (MEN) type 1 over a 3-year period were noted to have these lesions.<sup>3</sup> Shagreen patches of tuberous sclerosis are collagenomas, and collagenomas have also been associated with Down syndrome. Other diseases associated with collagenomas include chronic myelocytic leukemia, syphilis, Cowden disease,

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Proteus syndrome,

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and encephalocraniocutaneous lipomatosis.

- Familial cutaneous collagenoma: Familial cutaneous collagenoma (FCC) is an inherited disorder. Lesions typically occur in the postpubertal period. Increased numbers of lesions during

pregnancy have been reported in a few patients. <sup>6</sup> Cardiac disease has been associated with FCC.

- Shagreen patch: Shagreen patch is a collagenoma variant associated with tuberous sclerosis, a disease most commonly inherited in an autosomal dominant pattern. The genetic defects are in the *TSC1* and *TSC2* genes, which produce hamartin and tuberin, respectively. Flesh-colored plaques of variable size are primarily located in the lumbosacral area. They can occur singularly or asymmetrically in limited numbers.

- Eruptive collagenoma: This is one of the acquired variants of collagenoma characterized by nodules similar to those of FCC.

- Isolated collagenoma: This is characterized by nonfamilial hamartomas of the collagen type.

- Plantar cerebriform collagenoma: This is a disorder that can be inherited or develop sporadically. It is one of the most characteristic findings in persons with Proteus syndrome, in whom it appears in the first or second year of life.

- Buschke-Ollendorf syndrome: Buschke-Ollendorf syndrome is a genodermatosis characterized by abnormalities of the skin and the bone. It is inherited in an autosomal dominant fashion. Skin lesions, referred to as dermatofibrosis lenticularis disseminata, typically arise before puberty and can be present at birth. Bone lesions of osteopoikilosis are asymptomatic and of no pathologic significance.

- Nevus anelasticans: This condition is not inherited. Elastomas can occur during childhood or in early adolescence.

- Juvenile elastoma: These develop in a sporadic fashion.

- Nevus elasticus: This is an elastoma that is an acquired condition.

- Nevus mucinosis (Hunter syndrome)<sup>7</sup>: These lesions appear before age 10 years and can disappear spontaneously. Hunter syndrome is a lysosomal storage disorder usually inherited in an X-linked recessive pattern; however, a less frequent autosomal recessive pattern has been noted. The etiology of Hunter syndrome is the lack of iduronate sulfatase, leading to the accumulation of the mucopolysaccharides dermatan sulfate and heparan sulfate.

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Patients should receive a complete physical examination to rule out any associated conditions.

- FCC: Multiple, indurated cutaneous papulonodules that vary in size are located over the upper two thirds of the back

Shagreen patch: Flesh-colored plaques of variable size are located singularly or asymmetrically in limited numbers in the lumbosacral area

- Eruptive collagenoma: Multiple cutaneous papulonodules are located on the extremities, the lower part of the trunk, and the ears.
- Isolated collagenoma: This condition is characterized by cutaneous papulonodules, sometimes in a zosteriform pattern. Note the image below.
- Plantar cerebriform collagenoma: This condition is characterized by cerebriform plaques on the palms and the soles.
- Buschke-Ollendorf elastomas: Lesions consist of minimally elevated and firm nodules that may be grouped together in one or several plaques, or they may be widely disseminated. They vary in size from 0.5-8 cm in diameter, and they may have a wrinkled, pigskin appearance. The most common areas of involvement include the abdomen, the back, the buttocks, the arms, and the thighs. Nevi are asymmetric and occur on the lower part of the trunk and the extremities.
- Nevus anelasticans: These small, yellowish, perifollicular papules lack elastic fibers. They are located on the chest.
- Juvenile elastoma: Numerous nodules are present on the lower part of the trunk and the anterior aspects of the thighs.
- Nevus elasticus: Lesions are similar to those of juvenile elastoma.
- Nevus mucinosis (Hunter syndrome): Symmetric, small, firm papules that are located on the arms, on the chest, and over the scapular region give the skin a pebbled appearance. Hunter syndrome involves multiple organ systems, including severe CNS impairment (eg, mental retardation, deafness, progressive neurologic disease), coronary heart disease, hepatosplenomegaly, and respiratory disease. It is also associated with coarse facial features.

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The cause of connective tissue nevi is unknown

- - Laboratory studies are usually directed by signs or symptoms suggesting that the connective tissue nevus is part of an underlying syndrome. Eruptive connective tissue nevi have been associated with syphilis.
  - Hunter syndrome can be detected either by performing fibroblast enzyme studies or by finding mucopolysaccharides in the urine.
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- Radiographs of the spine should be obtained in patients with extensive musculoskeletal deformities.
  - In patients suspected of having Buschke-Ollendorf syndrome, radiographs of the hands, the feet, and the knees should be obtained. In patients with Buschke-Ollendorf syndrome, radiographic studies reveal round densities that are 2-10 mm in diameter in the long bones and the bones of the hands, the feet, and the pelvis.
  - In patients with tuberous sclerosis, imaging studies of the brain, EEG, fundoscopic examination, renal ultrasound, and an echocardiogram in infancy are indicated.
  - Cardiac studies, such as echocardiography, are useful to evaluate for coronary heart disease secondary to mucopolysaccharide deposition.
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- Perform either a punch biopsy or an incisional/excisional skin biopsy. The skin biopsy depth must include the entire dermis and may need to include adjacent healthy skin to document abnormalities in elastin, collagen, or ground substance.

## Histologic Findings

In collagenoma, a disproportionate increase of dense, coarse collagen fibers, leading to dermal thickening, is observed. Storiform collagenomas have been suggested to be a possible clue to a diagnosis of Cowden disease. Scanning electron microscopy of the dermis of an eruptive collagenoma showed individualized collagen fibers forming waved compact masses and not bundles. Transmission electron microscopy also showed sparse and loose collagen fibers with different diameters in cross sections.<sup>8</sup>

In elastoma, the dermis has an increased number of nonfragmented, interweaving elastin fibers.

In pseudoxanthoma elasticum, elastic tissue fragmentation and calcification are observed.

Hunter syndrome is the only mucopolysaccharidosis in which significant extracellular dermal mucin is present. The fibroblasts in this condition metachromatically stain cytoplasmic material, and characteristic vacuoles are seen on electron microscopy examination.

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A biopsy may be indicated for diagnostic purposes. One case report has described a linear nodular collagenoma treated successfully with intralesional triamcinolone.<sup>9</sup>

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Surgical excision is necessary when the patient would like the lesion removed for cosmetic reasons; however, surgery may not be advised when multiple or large lesions are present.

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For connective tissue nevi unassociated with a syndrome, no additional consultation is required.

- Internal medicine/pediatric specialists: Patients with tuberous sclerosis, Proteus syndrome, or Hunter syndrome may have multiple organ system involvement and should receive a complete medical evaluation.
- Orthopedic surgeon: A bone biopsy may be needed to determine the nature of the bony lesions in patients with suspected Buschke-Ollendorf syndrome. Patients with Buschke-Ollendorf syndrome may also develop joint contractures over areas of melorheostosis. Patients with Hunter syndrome should be screened for musculoskeletal involvement.
- Neurologist: Patients with tuberous sclerosis and Hunter syndrome should be screened for CNS involvement.
- Ophthalmologist: Patients with tuberous sclerosis may have retinal hamartomas.