Botryoid connective tissue nevi: An uncommon presentation of hamartoma of the skin

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INTRODUCTION

Connective tissue nevi (CTN) are hamartomas of the skin, resulting from a malformation of the dermis, by increase or alteration of one or more components of the extracellular matrix. A first classification of CTN was established in 1980 by Uitto et al[1] based on the type of component involved. Following the discovery of new patterns of CTN, McCuaig et al[2] proposed a revisited classification in 2012.

The incidence of CTN is unknown, and the disease is probably underdiagnosed. The diagnosis is often established in early childhood.[3] Classically, CTN appear as firm, asymptomatic, flesh-colored or yellowish papules or nodules of the dermis. Sometimes, they may have a tumor-like appearance. CTN are most often found on the trunk and extremities. In the majority of the cases, lesions are solitary and localized,[3] but disseminated lesions may be observed.[4] CTN can be congenital or acquired, sporadic or inherited,[2] and may also be part of a syndrome.

There is a large variability in the clinical and histologic presentation of CTN.[5]

We describe a rare case of CTN with an unusual botryoid presentation.

CASE REPORT

We report the case of a 1-year-old child referred to the dermatology department for a congenital lesion of the left thigh, which had gradually increased. The lesion was clinically soft, papillomatous, not infiltrated, and asymptomatic (Fig 1). There was no other anomaly on clinical examination. In particular, neurologic examination was normal, and there was no associated deafness. Microcystic lymphatic malformation was initially suspected, and an ultrasound examination was performed, consistent with this diagnosis. However, the lesion subsequently increased in size (Fig 2) and was complicated by local infection. Magnetic resonance imaging revealed a lesion strictly localized in the skin. Surgical management was decided.

Abbreviations used:

CTN: connective tissue nevi
RMS: rhabdomyosarcoma

Histologic examination (Fig 3) revealed a malformation of the dermis, involving an increase in a contingent of small spindle cells; poorly differentiated, with a relatively regular nucleus, and of striated muscle origin (desmine$^+$, myogenin$^+$). This was associated with the presence of multiple small buds located in the dermis containing numerous vessels and with a botryoid pattern. Immunohistochemical analysis excluded sarcoma (PAX5$^-$), hemopathies (CD3$^-$, CD20$^-$, and MPO$^-$) and Kaposi disease (HHV8$^-$). Because of the increase of striated muscle cells, and despite the negativity of the marker PAX5 in the immunohistochemical analysis, genetic

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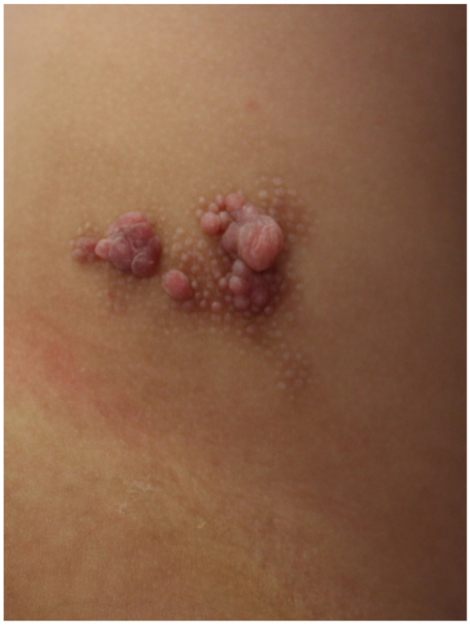

Fig 1. A soft and papillomatous lesion of the left thigh.

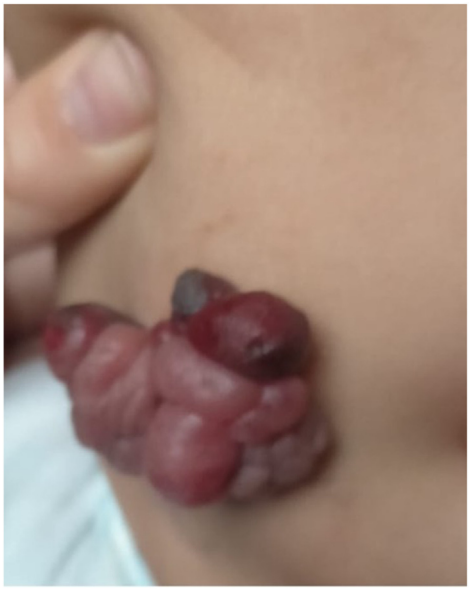

Fig 2. An increase in the size of the lesion during follow-up.

analysis was carried out so as not to disregard a diagnosis of rhabdomyosarcoma (RMS). Molecular biology analysis did not reveal any genomic alteration, ruling out the hypothesis of a botryoid RMS. The final diagnosis retained was botryoid CTN because of the increase in a benign contingent of striated muscle with a botryoid pattern. The clinical course was favorable after resection without recurrence.

DISCUSSION

CTN are benign tumors of the skin and include a large spectrum of different clinical and histologic presentations. Although the 3 main components usually found in CTN are collagen, elastin, and proteoglycans, other components can also be involved, including fibroblastic or cellular components.[6]

In our case, the histology of the lesion was surprising, because of the presence of a botryoid pattern, which, to our knowledge, has never been described before. This histologic presentation required the exclusion of the differential diagnosis of a botryoid RMS, which has a radically different prognosis and management.[7] Indeed, RMS is the most common soft-tissue sarcoma in children[8] and corresponds to a malignant tumor. It is frequently characterized by an asymptomatic mass, localized on the head, the genito-urinary tract, or the extremities. Nevertheless, symptoms may appear by compression of adjacent structures. There are several histologic subtypes,[9] with the botryoid pattern being a rare variant of RMS. In cases of botryoid RMS, the clinical aspect may be a papillomatous lesion, usually localized on the mucous membranes.[10] The major risk of this disease is the appearance of metastases, and the overall survival at 5 years is estimated at 70%; hence the need for a rapid diagnosis. However, in our case, the absence of genetic alteration allowed us to eliminate this hypothesis and to make the final diagnosis of botryoid CTN (Table I).

Even if it is a benign malformation, a diagnosis of CTN must lead to rigorous medical history taking and clinical examination, as these tumors may be indicative of a syndromic disease, such as Buschke-Ollendorff syndrome, proteus syndrome, tuberous sclerosis complex, or multiple endocrine neoplasia type 1.[5] The clinical examination should include a search for symptoms, such as neurologic disorders, deafness, or other associated skin lesions, as the presence of one of these signs may guide the diagnosis toward a syndromic form of CTN.

There is no consensus regarding treatment.[5] Treatment is selected after considering CTN subtype, the number and location of the lesions, and the age of the patient. Surgery is the most frequent treatment modality reported, as in our case, because the lesion was complicated by an infection and developing rapidly. Alternative therapeutic options for usual subtypes are laser, intralesional injection of corticosteroid, or therapeutic abstention.

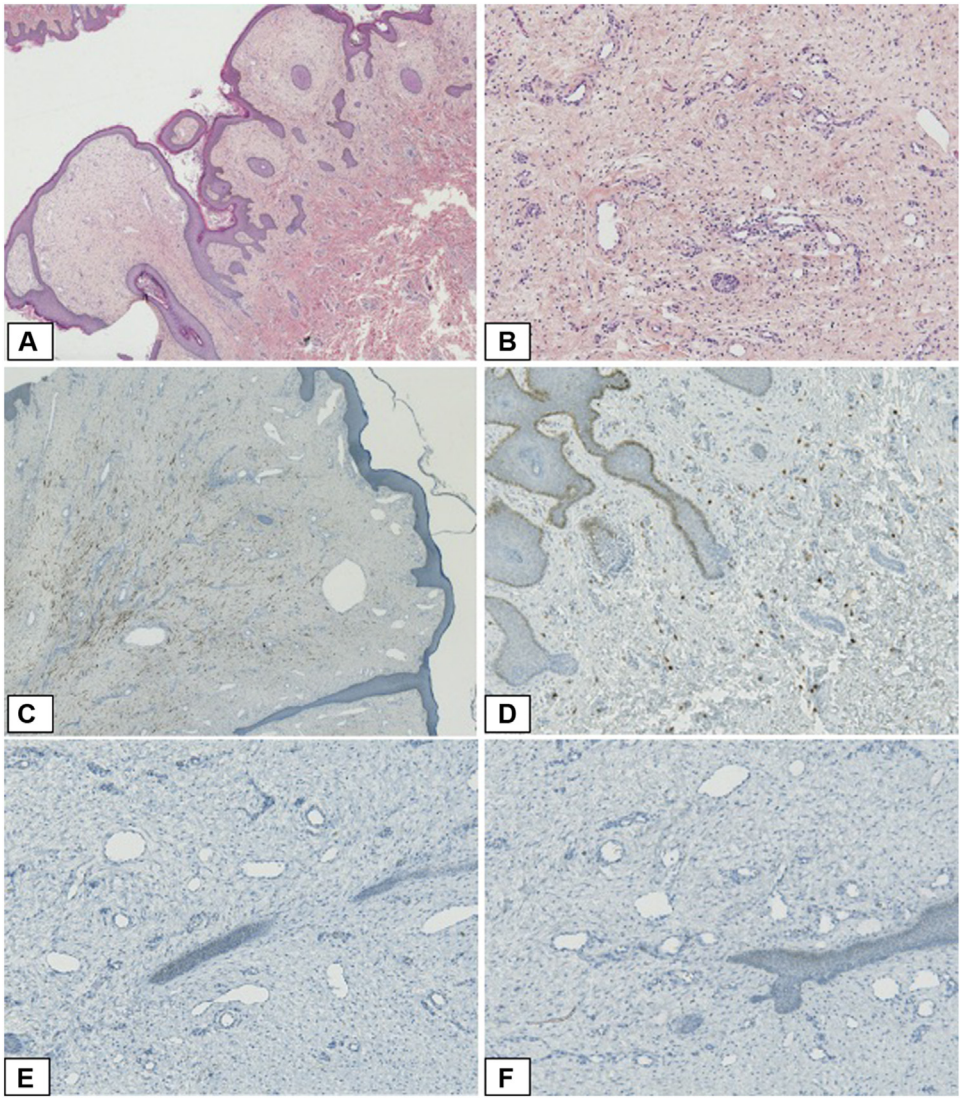

Fig 3. Skin biopsy. Multiple small buds were located in the dermis, with a botryoid pattern and containing numerous vessels. There was an association with small spindle cells of striated muscle differentiation. (**A,** and **B,** Hematoxylin-eosin stain; original magnification: **A,** ×2; **B,** ×40. **C,** Desmine^{+} stain. **D,** Myogenin^{+} stain. **E,** PAX5^{-}stain. **F,** HHV8^{-}stain.)

In conclusion, we report a rare case of botryoid CTN, which highlights the variability of presentation and the difficulty of making the diagnosis. The final diagnosis was based on histologic findings. In our case, complete surgical removal was required because of the rapid development and the initial diagnostic doubt.

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Table I. Characteristics of connective tissue nevi, botryoid-subtype connective tissue nevi, and rhabdomyosarcoma

Characteristics	CTN	Botryoid-subtype CTN	RMS
Epidemiology	Frequency unknown, probably underestimated Early childhood (0-5 yrs) Type: sporadic lesions > inherited condition; acquired > congenital	Uncommon presentation One-year-old child Sporadic lesion	Most common type of soft-tissue sarcoma in children (6 cases/million inhabitants/y) Peak incidence: early childhood (2-6 yrs) and adolescence (10-18 yrs) Sporadic form > familial syndromes
Histology	Increase or alteration of one or more components of the extracellular matrix of the dermis Main components: collagen, elastin, and proteoglycan Rarely: fibroblastic or cellular	Increase in spindle cells of striated muscle origin (cellular component) in the dermis Association with multiple small buds, located in the dermis, and containing multiple vessels, with a botryoid pattern IHC: desmine^{+}, myogenin^{+}, PAX5^{-}, CD3^{-}, CD20^{-}, MPO^{-} Molecular biology: absence of genomic alteration	Infiltrate of malignant cells of striated muscle origin Main histologic subtypes: embryonal > alveolar > spindle/sclerosing > pleomorphic Botryoid subtype: rare variant of embryonal type IHC: desmine^{+}, myogenin$^{+/-}$, MyoD1$^{+/-}$ Molecular biology: genomic alterations
Clinical aspects	Firm and asymptomatic papules, flesh-colored or yellowish Sites: trunk, extremities Solitary and localized lesions > multiple lesions	Soft and asymptomatic, flesh-colored lesion, with a grape-like appearance Localized on the thigh Solitary lesion	Asymptomatic mass or symptomatic by compression of adjacent structures Sites: head and neck region, genito-urinary tract, extremities RMS botryoid: grape-like appearance, usually localized in mucous membranes
Clinical course	Benign course, usually without complication Treatment: no consensus, often surgery without recurrence	Rapid extension in size Absence of recurrence after surgery	Risk of metastases Treatment: association of chemotherapy, surgery, and radiotherapy Overall survival at 5 years: 70%

CTN, Connective tissue nevi; *IHC,* immunohistochemistry; *RMS,* rhabdomyosarcoma.

Conflicts of interest

None disclosed.

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