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3 **Title:** Botryoid Connective Tissue Nevi: an uncommon presentation of hamartoma of the skin

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33 INTRODUCTION

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35 Connective tissue nevi (CTN) are hamartomas of the skin, resulting from a malformation of
36 the dermis, by increase or alteration of one or more components of the extracellular matrix. A
37 first classification of CTN was established in 1980 by Uitto et al¹ based on the type of
38 component involved. Following the discovery of new patterns of CTN, McCuaig et al²
39 proposed a revisited classification in 2012.

40 The incidence of CTN is unknown with probably an underdiagnosis of this disease. The
41 diagnosis is often made in early childhood.³ Classically, CTN appear as firm, asymptomatic,
42 flesh-colored or yellowish papules or nodules of the dermis. Sometimes, they may have a
43 tumoral-like appearance. CTN are most often found on the trunk and extremities. In the
44 majority of cases, lesions are solitary and localized,³ but disseminated lesions are possible.⁴
45 CTN can be congenital or acquired, sporadic or inherited,² and may also be part of a
46 syndromic form.

47 There is a large variability in the clinical and histological presentation of CTN.⁵

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

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58 **CASE REPORT**

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

68 Histological examination (Figure 3) showed a malformation of the dermis by increase in a
69 contingent of small spindle cells, poorly differentiated, with a relatively regular nucleus, of
70 striated muscle origin (Desmine+, Myogenin +). This was associated with the presence of
71 multiple small buds located in the dermis and containing numerous vessels, with a botryoid
72 pattern. Immunohistochemical (IHC) analysis excluded sarcoma (PAX5-), hemopathies
73 (CD3-, CD20- and MPO-) and Kaposi's disease (HHV8-). Due to the increase of striated
74 muscle cells, and despite the negativity of the marker PAX5 in IHC, genetic analysis was
75 carried out so as not to disregard a diagnosis of rhabdomyosarcoma (RMS). Molecular
76 biology analysis did not reveal genomic alteration, ruling out the hypothesis of a botryoid
77 RMS. The final diagnosis retained was a botryoid CTN because of the increase in a benign
78 contingent of striated muscle with a botryoid pattern. The evolution was favorable after
79 resection without recurrence.

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83 **DISCUSSION**

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85 CTN are benign tumors of the skin and include a large spectrum of different clinical
86 and histological presentations. Although the three main components usually found in CTN are
87 collagen, elastin and proteoglycans, other components can also be involved, including
88 fibroblastic or cellular components.⁶

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90 In our case, the histology of the lesion was surprising, because of the presence of a
91 botryoid pattern, which, to our knowledge, has never been described before. This histological
92 presentation required the exclusion of the differential diagnosis of a botryoid RMS, which has
93 a radically different prognosis and management.⁷ Indeed, RMS is the most common soft
94 tissue sarcoma in children⁸ and corresponds to a malignant tumor. It is frequently
95 characterized by an asymptomatic mass, localized on the head, the genito-urinary tract, or the
96 extremities. Nevertheless, symptoms may appear by compression of adjacent structures.
97 There are several histological subtypes,⁹ with the botryoid pattern being a rare variant of
98 RMS. In cases of botryoid RMS, the clinical aspect may be a papillomatous lesion, usually
99 localized on the mucous membranes.¹⁰ The major risk of this disease is the appearance of
100 metastases, and the overall survival at 5 years is estimated at 70%, hence the need for a rapid
101 diagnosis. However, in our case, the absence of genetic alteration allowed us to eliminate this
102 hypothesis and to make the final diagnosis of botryoid CTN (Table I).

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104 Even if it is a benign malformation, a diagnosis of CTN must lead to rigorous medical
105 history taking and clinical examination, as these tumors may be indicative of a syndromic
106 disease, such as Buschke-Ollendorf syndrome (BOS), proteus syndrome, tuberous sclerosis

107 complex (TSC),⁵ or multiple endocrine neoplasia type 1 (MEN1).⁵ The clinical examination
108 should include a search for symptoms such as neurological disorders, deafness or other
109 associated skin lesions, as the presence of one of these signs may guide the diagnosis towards
110 a syndromic form of CTN.

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

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118 In conclusion, we report a rare case of botryoid CTN, which highlights the variability of
119 presentation and the difficulty of making the diagnosis. The final diagnosis was based on
120 histological findings. In our case, complete surgical removal was required due to the rapid
121 evolution and the initial diagnostic doubt.

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129 **Abbreviations**

130 **BOS:** Buschke-Ollendorf syndrome

131 **CTN:** Connective Tissue Nevi

132 **IHC:** Immunohistochemistry

133 **MEN1:** Multiple Endocrine Neoplasia type 1

134 **MRI:** Magnetic Resonance Imaging

135 **RMS:** Rhabdomyosarcoma

136 **TSC:** Tuberous Sclerosis Complex

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211 **Figure Legend**

212 **Figure 1:** Soft and papillomatous lesion of the left thigh

213 **Figure 2:** Increase in size of the lesion during the follow-up

214 **Figure 3:** Skin biopsy. Multiple small buds located in the dermis, with a botryoid pattern,
215 containing numerous vessels. Association with small spindle cells of striated muscle
216 differentiation. A, Hematoxylin-eosin stain; original magnification x 2. B, Hematoxylin-eosin
217 stain; original magnification x 40. C, Desmine⁺ stain. D, Myogenin⁺ stain. E, PAX5⁻ stain. F,
218 HHV8⁻ stain.

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234 **Table I:** Characteristics of connective tissue nevi, botryoid connective tissue nevi, and

235 rhabdomyosarcoma

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	Connective Tissue Nevi	Connective Tissue Nevi with botryoid subtype	Rhabdomyosarcoma
Epidemiology	<ul style="list-style-type: none"> - Frequency unknown, probably underestimated - Early childhood (0-5 years) - <u>Type:</u> sporadic lesions > inherited condition; acquired > congenital 	<ul style="list-style-type: none"> - Uncommon presentation - One-year-old child - Sporadic lesion 	<ul style="list-style-type: none"> - Most common type of soft tissue sarcoma in children (6 cases/ million inhabitants/year) - <u>Peak incidence:</u> early childhood (2-6 years) and adolescence (10-18 years) - Sporadic form > familial syndromes
Histology	<ul style="list-style-type: none"> - Increase or alteration of one or more components of the extracellular matrix of the dermis - <u>Main components:</u> collagen, elastin, and proteoglycane - <u>Rarely:</u> fibroblastic or cellular 	<ul style="list-style-type: none"> - 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 - <u>IHC:</u> Desmine +, Myogenin +, PAX5 -, CD3 -, CD20 -, MPO - - <u>Molecular biology:</u> absence of genomic alteration 	<ul style="list-style-type: none"> - Infiltrate of malignant cells of striated muscle origin - <u>Main histological subtypes:</u> embryonal > alveolar > spindle/sclerosing > pleomorphic - <u>Botryoid subtype:</u> rare variant of embryonal type - <u>IHC:</u> Desmine +, Myogenin +/-, MyoD1 +/- - <u>Molecular biology:</u> genomic alterations
Clinical aspects	<ul style="list-style-type: none"> - Firm and asymptomatic papules, flesh-colored or yellowish - <u>Sites:</u> trunk, extremities - Solitary and localized lesions > multiple lesions 	<ul style="list-style-type: none"> - Soft and asymptomatic, flesh-colored lesion, with a grape-like appearance - Localized on the thigh - Solitary lesion 	<ul style="list-style-type: none"> - Asymptomatic mass or symptomatic by compression of adjacent structures - <u>Sites:</u> head and neck region, genitourinary tract, extremities - <u>RMS botryoid:</u> grape-like appearance, usually localized in mucous membranes
Evolution	<ul style="list-style-type: none"> - Benign evolution, usually without complication - <u>Treatment:</u> no consensus, often surgery without recurrence 	<ul style="list-style-type: none"> - Rapid extension in size - Absence of recurrence after surgery 	<ul style="list-style-type: none"> - Risk of metastases - <u>Treatment:</u> association of chemotherapy, surgery, and radiotherapy - Overall survival at 5 years: 70 %

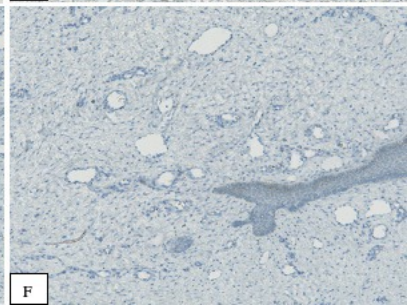
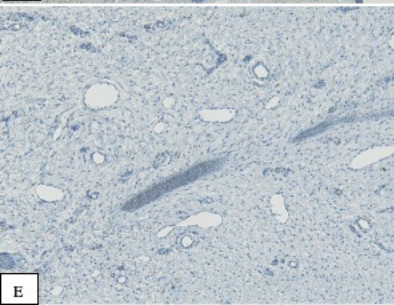
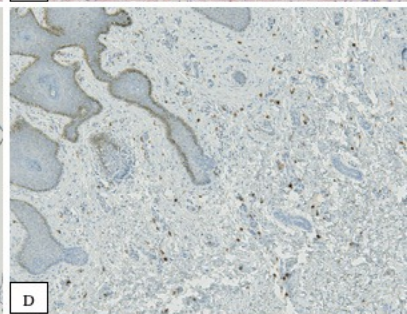
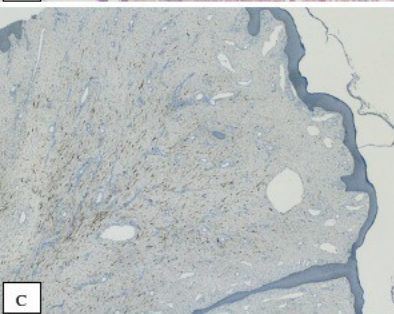
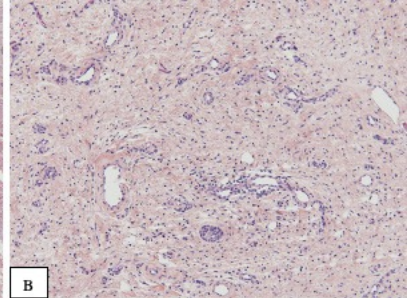
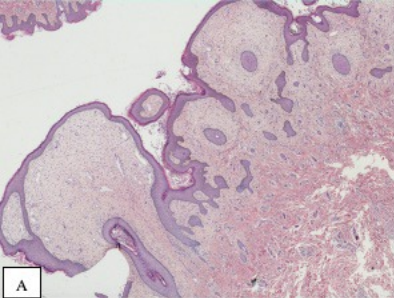
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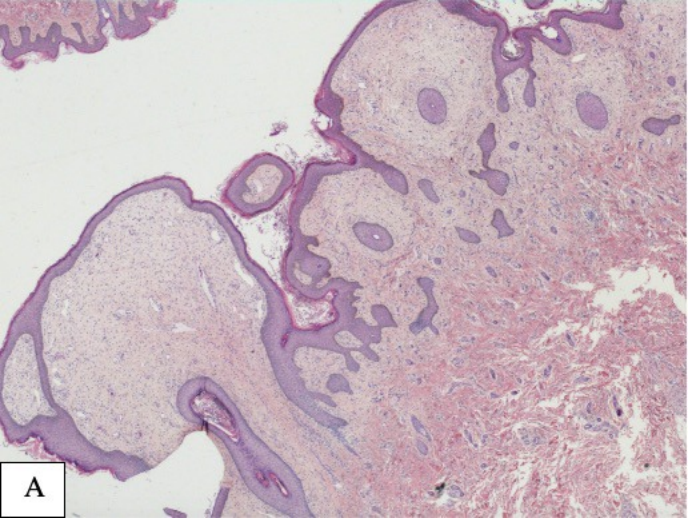
238 IHC: immunohistochemistry; RMS: rhabdomyosarcoma

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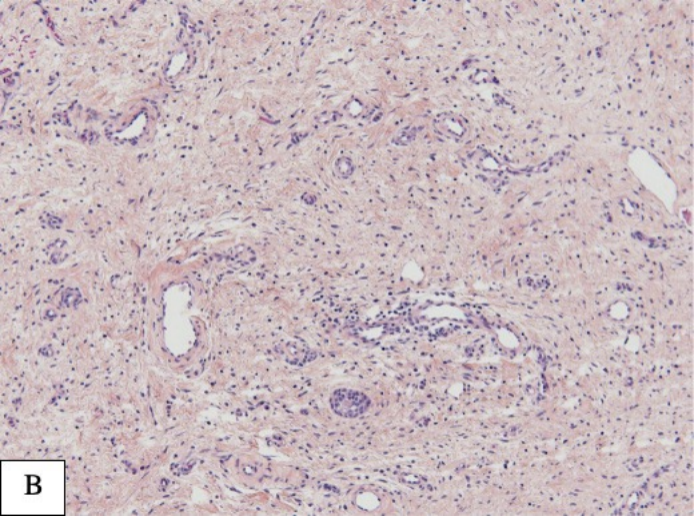




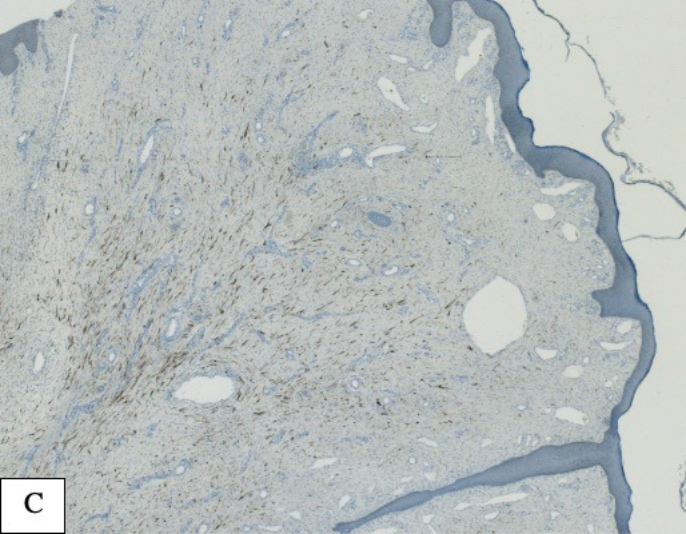




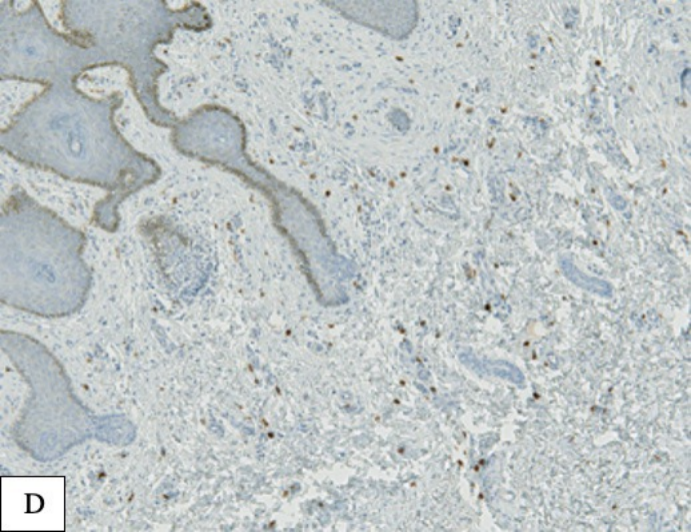
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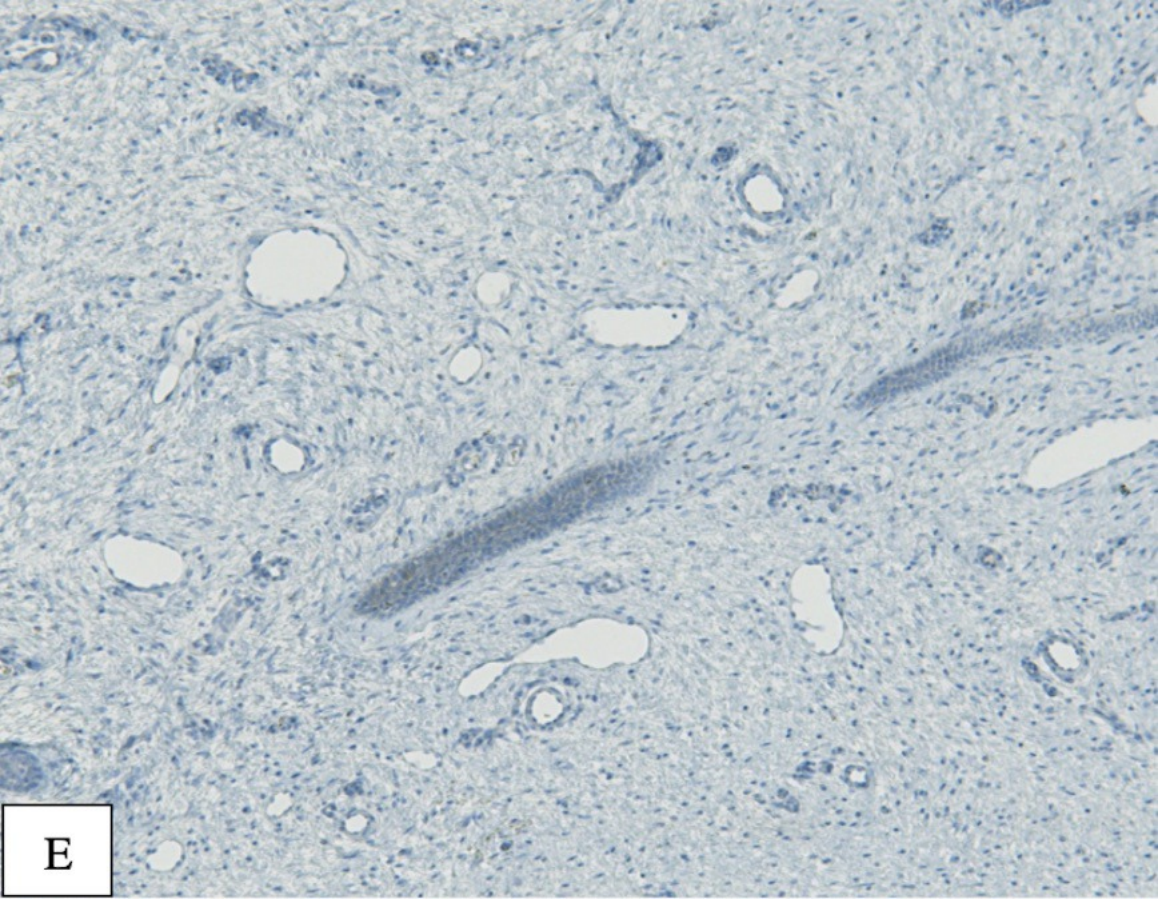
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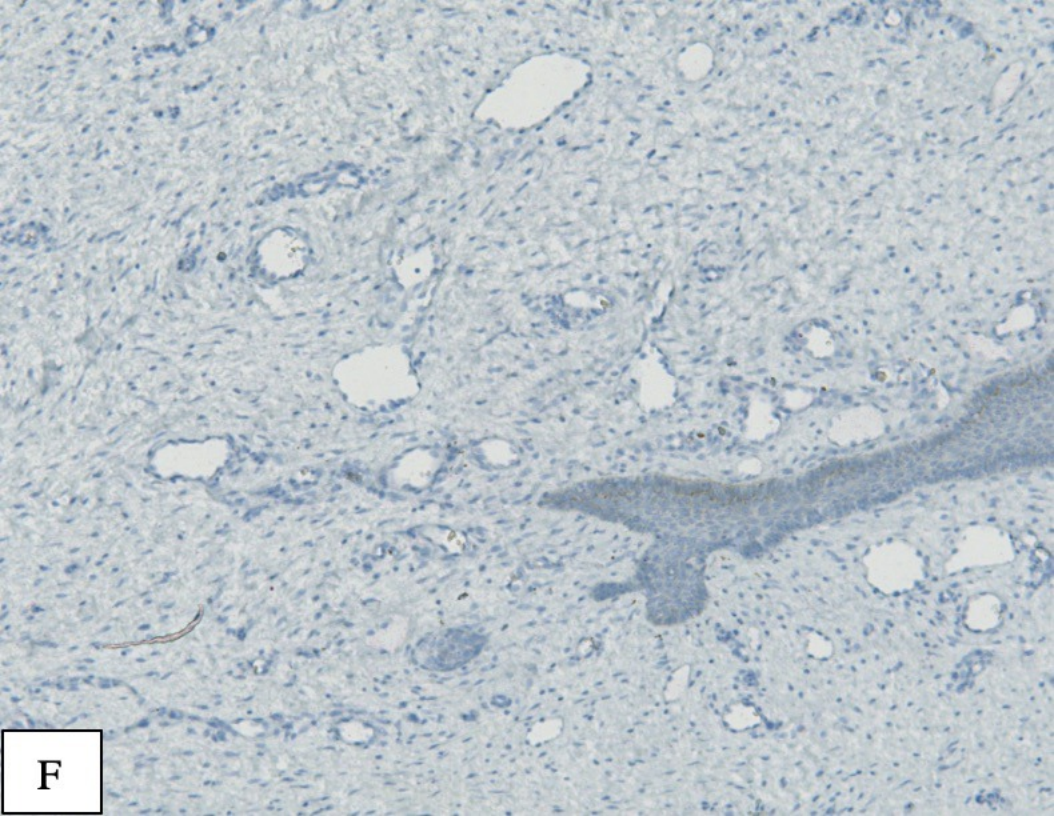
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