CASE REPORT

RJME
Romanian Journal of Morphology & Embryology
http://www.rjme.ro/

Unusual variant of blue nevus associated with dermatofibromas

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Abstract

The blue nevus is a variant of a melanocytic nevus that presents as blue-gray to blue or black papules or nodules measuring up to 1 cm in diameter; it has a predilection for females and can be congenital or acquired. The classification of blue nevi is complex, with biological behavior being benign, borderline, or malignant. The case we present is one of a 40-year-old woman with multiple dermatofibromas that appeared and increased gradually in size during pregnancy. Physical examination revealed three spherical, brownish to red-purple nodules localized on the left leg, right shoulder and right laterocervical area. In addition, on her right forearm, there was a 0.3 cm nodule with a discreet non-pigmented, elevated area and a blue perilesional border that appeared in her childhood, affirmative after stinging herself with a pencil. The patient's family history was negative for significant lesions. The laboratory and imagistic findings were normal. Four skin biopsies were performed. The histopathological examination revealed an uncommon blue nevus with two different populations of pigmented cells: spindle shaped or dendritic melanocytes diffuse distributed in the middle dermis and closely aggregated deeply pigmented melanocytes in the reticular dermis. The other three lesions were diagnosed as dermatofibromas: bland spindle shaped cells in a fibrous stroma, some cells with a storiform arrangement. The overlying epidermis was hyperplastic with acanthosis and hyperpigmentation of the basal cell layer. No mitoses were seen.

Keywords: epithelioid blue nevus, sclerosing variant, dermatofibromas, dermal melanocytosis.

Introduction

Blue nevus is a variant of dermal melanocytosis, a benign phenomenon that includes Mongolian spot, nevi of Ota, Ito, Hori and Sun, neurocristic hamartoma and acquired dermal melanocytosis [1].

The dermal melanocytosis originate by the accumulation of melanocytes in the dermis, arrested during their migration from neural crest to the epidermis [2].

Dermal melanocytosis is poorly or well-circumscribed lesion both clinical and histological, depending on different types, and can be congenital or acquired. Sometimes, its appearance is nevoid [3].

Histopathological, dermal melanocytosis was described as a presence of melanin in the dermis. The melanin granules are found in the cytoplasm of melanophages and dendritic dermal melanocytes. Moreover, it can be observed extracellular melanin distributed free between collagen bundles of the dermis [4].

Because of the similar histopathology, composed of dendritic dermal melanocytes, the differential diagnosis of different dermal melanocytosis subtypes is often made after clinical correlation. The blue nevus, because of its unique histologic appearance, is an exception from this rule [4].

Dermatofibroma is a common benign condition that usually appears as an isolated lesion. Rarely it occur as multiple dermatofibromas, the term being for the first time used in 1970 by Baraf CS and Shapiro L and defined as 15 dermatofibromas appeared in few months [5]. More recently, the definition was changed in five to eight lesions in four months [6]. If initially the multiple dermatofibroma was described as isolated, nodular tumor all over the body, in 1984, Dupré A *et al.* presented a study about multiple clustered dermatofibromas [7, 8].

Histological, dermatofibromas are tumors composed of bland spindle cells disposed in whorls and interspersed in bundles of thick collagen [7].

Patient, Methods and Results

A 40-year-old woman presented herself to the Department of Dermatology, Emergency City Hospital of Timişoara, Romania, for multiple (three) lesions disseminated in different segments of the body that appeared six years earlier. The first nodule appeared on the left leg, in the tenth week of pregnancy. In the next four months, it was followed by other two similar lesions in different regions of the body (right shoulder and right laterocervical area) that increased gradually in size during pregnancy.

Past medical history included three ovarian stimulations with fertility drugs during a controlled *in vitro* fertilization program. There were no signs of ovarian hyperstimulation and the third treatment was successful.

The patient's family history was negative for significant lesions.

Physical examination revealed three spherical, brownish to red-purple nodules. The lesions ranged in size from 5 to 11 mm and were localized on the left leg (lesion 1), right shoulder (lesion 2) and right latero-cervical area (lesion 3). The nodules were incompressible, mobile and tender upon palpation. No pain was described, except during the time of growing.

In addition, on her right forearm, there was a 0.3 cm small-circumscribed blue nodular lesion, with a slightly elevated, non-pigmented, central area and perilesional blue border that appeared in her childhood, affirmative after stinging herself with a pencil.

The laboratory and imagistic findings were normal.

Because of the appearance of nodules during pregnancy and their rapid growth, the clinician decided to excise them, including the blue lesion. Four skin biopsies were performed.

The specimens were fixed in 4% (v/v) formalin and embedded in paraffin. Three micrometers thick serial sections were stained with Hematoxylin–Eosin. The cut surface of the blue lesion from the right forearm, revealed a brown blackish lesion with a bluish tint.

On histological examination, the dome-shaped nodule was composed of bipolar and dendritic melanocytic cells and melanophages, which extend from the papillary dermis to the subcutaneous fat, with two different patterns, one nodular in the deep dermis and another one diffuse in the middle and papillary dermis (Figure 1).

In the deep dermis, there was a very well circumscribed spherical collection of variably pigmented polygonal uniform melanocytic cells, with large vesicular nuclei and prominent eosinophilic nucleoli. The cells showed no pleomorphism. The pigmented dendritic processes intermingled with numerous heavily pigmented melanophages in a background of spindled and dendritic cells (Figure 2). The lesion involved the sweat glands (Figure 3) and arrector pili muscle (Figure 4). Mitoses were absent. No capsule was evident.

In the papillary and middle dermis, the dome-shaped lesion was hypopigmented and showed sclerosis (Figure 5). The sclerotic area was situated central and composed of only scattered residual bipolar and dendritic pigmented cells. On the sides, there was an admixture of heavily pigmented bipolar and dendritic cells and conspicuous melanophages in a dense fibrous stroma. The pigmented dendritic processes entrapped thickened bundles of collagen fibers (Figure 6). There was a condensation of interstitial dendritic pigmented cells in the perifollicular area with involvement of arrector pili muscle and neural infiltration (Figure 7). The globular melanocytes had one or two vesicular nuclei, with big nucleolus. Some of the nucleoli were eosinophilic. The cells showed no pleomorphism (Figure 8).

The diagnosis of sclerosing variant of an epithelioid blue nevus was established.

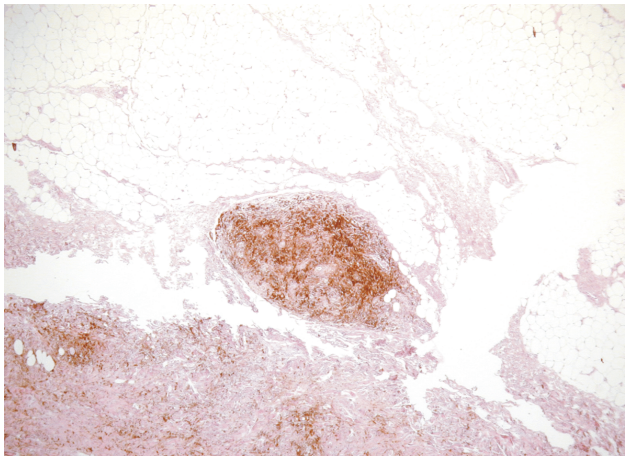

Figure 1 – ***The two components of blue nevus (HE stain, ob. 2×).***

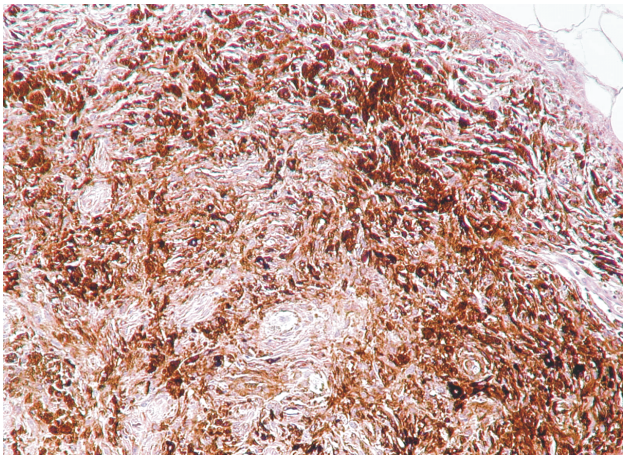

Figure 2 – ***Dermal well-circumscribed nodule, composed of heavily pigmented melanocytes (HE stain, ob. 10×).***

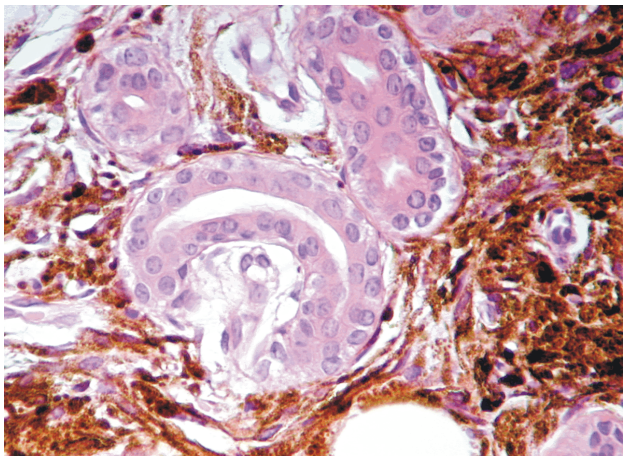

Figure 3 – ***Involvement of sweat glands units by heavily pigmented melanocytes (HE stain, ob. 40×).***

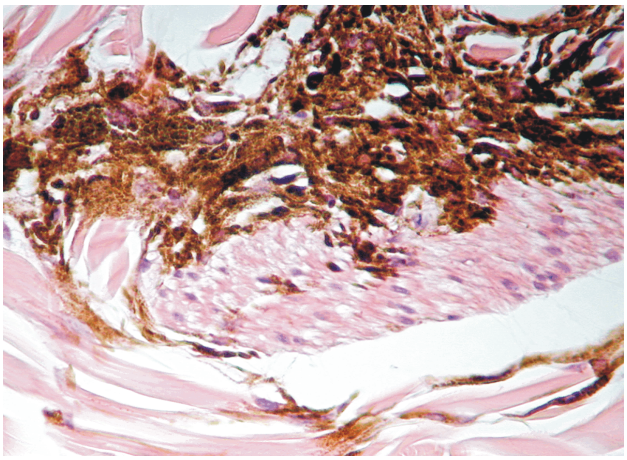

Figure 4 – ***Involvement of arrector pili muscle (HE stain, ob. 40×).***

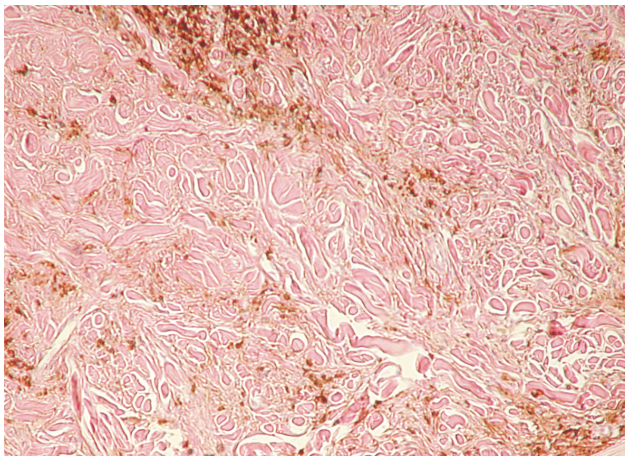

Figure 5 – ***Diffuse pattern of growth in the middle and papillary dermis (HE stain, ob. 10×).***

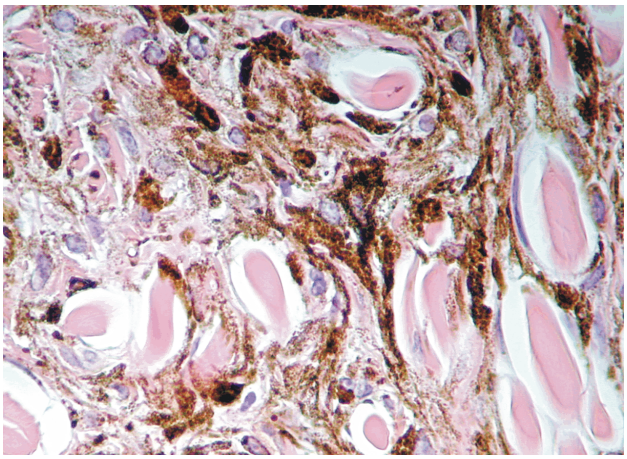

Figure 6 – ***Collagen bundles entrapped by dendritic processes of melanocytes (HE stain, ob. 40×).***

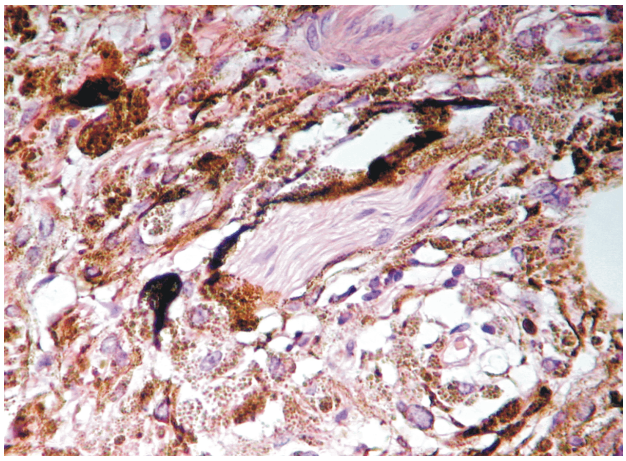

Figure 7 – ***Neural infiltration (HE stain, ob. 20×).***

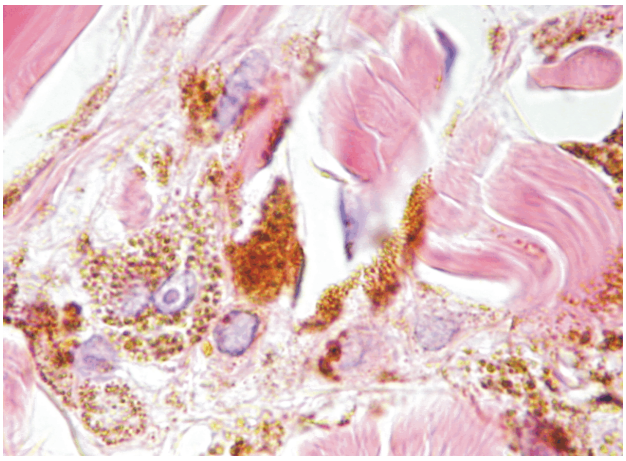

Figure 8 – ***Melanocytes with one or two nuclei and prominent eosinophilic nucleolus (HE stain, ob. 100×).***

The gross anatomy of the other three lesions revealed:

▪ Lesion 1: an unpigmented lesion, measuring 0.7 cm in diameter. The cut surface showed a pearly whitish lesion within the dermis and subcutaneous adipose tissue;

▪ Lesion 2: a flat, slightly pigmented lesion, 0.5 cm in diameter;

▪ Lesion 3: a sessile, pigmented, polypoid lesion, 1.1 cm in diameter.

The histopathology was similar for all the three lesions.

The tumor was observed from the papillary dermis to the cutaneous fat and was composed of bland spindle shaped cells in a fibrous stroma. In some areas, the cells had a storiform arrangement. The overlying epidermis was hyperplastic with acanthosis and hyperpigmentation of the basal cell layer. The tumor stroma was composed of thickened bundles of collagen fibers. At the periphery, the tumor had infiltrative borders with sheets of cells proliferating between the adipocytes of the subcutaneous tissue and entrapping collagen fibers. There were no mitoses.

The diagnosis of dermatofibroma was made.

Discussion

Tièche, a student of Jadassohn, first described the common blue nevus in 1906. Earlier authors described similar lesions as chromatophoroma and melanofibroma [9].

Although definitive experimental evidence is lacking, blue nevi are believed to represent dermal arrest in embryonal migration of neural crest melanocytes that fail to reach the epidermis. Collections of melanocytes can be found in fetal dermis, but they involutes during later gestation [10].

Because of the variation of blue nevi in different populations, a genetic predisposition has been suggested. However, familial cases of blue nevi are exceedingly rare. Common and cellular blue nevi have a predilection for females [10].

They are not associated with chromosomal aberrations, and show fewer B-RAF mutations compared with other nevi [11]. On the other hand, there were reported frequent somatic mutations in the heterotrimeric G protein alpha subunit, GNAQ, in blue nevi (83%), the same aspect seen in the ocular melanoma of the uvea (46%). The mutations occur exclusively in codon 209 in the *ras*-like domain and result in constitutive activation, turning GNAQ into a dominant acting oncogene [12].

Clinically, blue nevi can be single or multiple and usually affect the face and scalp, the backs of the hand and feet, the buttocks. Blue nevus frequently represents a blue or blue-black papule or nodule measuring up to 1 cm in diameter, the color being due to the depth of

melanin in the epidermis and the Tyndall effect. The skin around the lesion is also hyperpigmented [2].

Histopathological, there are some recognized variants of blue nevus: common blue nevus, epithelioid blue nevus, cellular blue nevus, atypical blue nevus and malignant blue nevus [2].

Common blue nevus may also been encountered in the conjunctiva, sclera, oral cavity, lymph nodes, breast, cervix, vagina, and prostate. Clinical variants include also targetoid and plaque-like blue nevi. It can be a dome-shaped heavily pigmented nodule containing pigmented bipolar dendritic cells intermingled with numerous melanophages. There is no pleomorphism and it may present at any level of the dermis. Occasional normal mitoses may be found and should not be misconstrued as implying malignant potential [13–17].

Histopathological, it was recognized a hypopigmented (sclerosing) variant of common blue nevus [18].

Epithelioid blue nevus is a rare variant. Initial it was described in children and young adults in association with Carney complex [19]. More recently, epithelioid blue nevus have been reported in the absence of this syndrome [20]. Focal epithelioid features can be observed in an otherwise typical common blue nevus. It can also affect conjunctiva and vulva [21]. Histopathological, the lesion appears as a spherical dermal nodule composed of variably pigmented polygonal cells with large vesicular nuclei and prominent eosinophilic nucleoli and heavily pigmented globular melanophages in a background of spindled and dendritic cells. Usually, the appendage is involved. The mitoses are occasional [2].

Cellular blue nevus is much rarer than the common variant. It is very important to recognize this variant because they may develop in melanoma. It may present at birth or develop in early adulthood. Clinically, the lesions are bigger than common variant, measuring up to 2 cm or more in diameter. The lesion may involve subcutaneous fat. The growth pattern can be nested, fascicular or alveolar, being composed of clear cells with pale cytoplasm and vesicular nuclei, and variably pigmented bipolar and dendritic cells. The mitoses are sparse or absent. The stroma may show hyalinization, cyst formation, and myxoid change. The neural infiltration may be present. There were described different variants: balloon cell-rich, desmoplastic, sclerosing and combined [22].

Our patient presented with many of these features. In the reticular dermis, we observed a nodule consistent with epithelioid variant of blue nevus. In the papillary dermis, the lesion showed sclerosis, similar to sclerosing variant of a common blue nevus. At all levels, the cells infiltrated skin appendage (sweat glands, arrector pilli muscle), already described in both variants, common and epithelioid. Moreover, we observed neural infiltration, described only, as far as we saw in the English literature, only in cellular blue nevus.

Atypical blue nevus is a common or cellular blue nevus with some degree of atypia, insufficient for malignancy but worrisome enough to be noted in pathological report. It has infiltrative lower border. The lesion is large and hypercellular. The atypical cells are isolated and never disposed in sheets or nodules. The mitotic activity is low (1–2 per 10 HPF), but no abnormal mitoses are seen. No foci of necrosis are observed [23].

Malignant blue nevus is an entity composed of melanoma arising in a common or cellular blue nevus or a melanoma mimicking cellular blue nevus in the absence of a precursor lesion. Malignant blue nevus is an aggressive tumor that can metastasize in lymph nodes, lung and liver [24–30].

The blue nevus with classical features does not require any treatment. For a solitary lesion, simple excision is usually curative. Rare cases of persistent blue nevi, manifesting as satellite lesions around the original excision site, have been reported. These must be distinguished from malignant blue nevus, and reexcision is recommended [2].

Differential diagnoses include dermatofibromas, tattoo reactions, nevi of Ota and Ito, melanoma.

The dermatofibroma represents one of the most common cutaneous soft tissue tumors. It occurs most often in the middle aged and shows a slight female predominance. The majority of lesions are located on the limbs or the trunk, slow growing and painless. It presents itself as a small raised, hyperkeratotic cutaneous nodules with a reddish – brown surface, usually less than 1 cm in diameter. Usually, it is easy to diagnose, problems with differential diagnosis only arise with its variants: cellular fibrous, aneurysmal, epithelioid, clear cell, palisading or atrophic dermatofibroma. Simple excision is usually curative. Local recurrence is exceptional except for some of the variants and in lesions occurring on the face. In some variants, rare metastases have been reported [31, 32].

In our patient, the histopathology of dermatofibroma is identical to those previously described in the literature, although the onset of the condition during pregnancy and after IVF treatment, combined with the appearance of three lesions in a short period, is noteworthy. We did not find in the English literature any case reported in association with ovarian drug stimulation.

Although at our patient appeared more than one dermatofibromas in a short period, the diagnosis of multiple dermatofibromas could not be established in accordance with the definition made by Baraf CS and Shapiro L in 1970 [5] and modified later by Ammirati CT *et al.* [6].

Conclusions

In this article, we presented a case of an epithelioid blue nevus with areas of sclerosis, skin appendage involvement and neural infiltration. We also highlighted an interesting appearance and presentation of dermatofibromas, a very common condition, but in this case in association with pregnancy and IVF treatment. The case is especially interesting, as the combination between sclerosing variant of a blue nevus and multiple dermatofibromas has never been documented.

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Received: December 15th, 2012

Accepted: April 25th, 2013