DERMATOLOGY PRACTICAL & CONCEPTUAL
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The long history of a melanoma associated with a congenital large plaque type blue nevus with subcutaneous cellular nodules

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Keywords: blue nevus, melanoma, congenital, large plaque type blue nevus with subcutaneous cellular nodules

Citation: Savoia F, Gaddoni G, Re G, Cristanti E. The long history of a melanoma associated with a congenital large plaque type blue nevus with subcutaneous cellular nodules. Dermatol Pract Concept 2015;5(3):4. doi: 10.5826/dpc.0503a04

Received: March 9, 2015; **Accepted:** June 8, 2015; **Published:** July 31, 2015

Funding: None.

Competing interests: The authors have no conflicts of interest to disclose.

All authors have contributed significantly to this publication.

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ABSTRACT The term large plaque type blue nevus with subcutaneous cellular nodules (LPTBN-SN) refers to a huge blue nevus, usually located on the trunk, that develops subcutaneous nodules many years after the lesion has appeared. The potential malignancy of an LPTBN-SN was only discovered in 2012.

We report the case of a 56-year-old Caucasian man that developed a cutaneous melanoma on an LPTBN-SN of the trunk. The first diagnosis was made more than 10 years before his death due to melanoma metastasis.

The case reported here highlights the malignant potential of an LPTBN-SN, the very long course even without treatment and the possible coexistence of benign, borderline or malignant subcutaneous nodules in the same LPTBN-SN.

Patients with large congenital blue nevi should be advised on the potential oncologic transformation of these lesions, the importance of follow-ups should be emphasized and, whenever possible, a preventive complete surgical removal should be evaluated before subcutaneous nodules develop.

Introduction

Blue nevus is considered a benign lesion that only in rare cases may progress into melanoma. The term "malignant blue nevus" includes both a melanoma that arose within a common or a cellular blue nevus or a de novo melanoma simulating a blue nevus [1].

A peculiar type of blue nevus is the so-called large plaque type blue nevus with subcutaneous cellular nodules (LPTBN-SN), a clinical variant characterized by large dimensions, plaque-like features, localization on the trunk, presence since birth or early childhood, and onset of discrete subcutaneous nodules many years later [2].

TABLE 1. Clinical and histological features of the different variants of blue nevi.

Variant	Clinical Features	Histological Features	Possible Evolution
Common blue nevus	A patch of blue-grey or blue-black pigmentation usually slightly raised and with a smooth surface; the diameters are usually less than 1 cm.	Bipolar and dendritic melanocytes are located in the dermis. The melanocytes tend to concentrate in the lower dermis, often around appendages or in the perivascular and perineural areas. Deeper tissues may be involved.	Reported, although very rare.
Cellular blue nevus	A patch of blue-grey or blue-brown pigmentation, raised, palpable and with a smooth surface; diameters are usually between 1 and 3 cm.	Bipolar and dendritic melanocytes are located in the dermis, but in addition there are islands of larger cells arranged in a neuroid or sarcomatoid fashion.	Reported, although rare.
Combined blue and acquired nevus	A patch of both blue and brown pigmentation, with atypical appearance.	Bipolar and dendritic melanocytes are located in the dermis, with additional dendritic cells in the overlying epidermis.	Not reported; lesions are benign but are usually excised because of the atypical clinical and dermoscopic features.
Sclerosing (desmoplastic) blue nevus	Firm, solitary, variably pigmented (usually grey-blue) papule or nodule.	Histological features are that of a typical blue nevus but in association with an exaggerated dermal fibrosis.	Not reported; differential diagnosis with melanoma may be difficult.
Epithelioid blue nevus / Pigmented epithelioid melanocytoma	The clinical features are the same of a common blue nevus. It can be associated with Carney complex. Epithelioid blue nevus and pigmented epithelioid melanocytoma are considered the same entity.	Variably pigmented epithelioid melanocytes with only a few melanophages and a few dendritic melanocytes.	Not reported.
Hypomelanotic / Amelanotic blue nevus	Firm, solitary, papule or nodule, usually flesh-coloured.	Histological features are that of a blue nevus, with dermal proliferation of spindle cells associated with variably desmoplastic stroma.	Not reported; differential diagnosis includes melanoma.
Large plaque type blue nevus	A huge blue nevus, usually located on the trunk, that develops subcutaneous nodules many years after the lesion has appeared.	The nodules are characterized by areas resembling common blue nevi and areas resembling cellular blue nevi, with infiltration of subcutaneous and soft tissues, including the fascia and the mammary tissue.	Reported, although rare.
Deep penetrating blue nevus	Deep blue or black papules or nodules, usually with irregular lateral margins; lesions are usually larger than common blue nevi.	Characteristic is the extension of nevus cells deep into the dermis, in a wedge shape, the base towards the epidermis. There are clusters of deep nevus cells throughout the dermis, frequently around the skin appendages. Cytology is characterized by a spindle cell population and mitotic figures are rare.	Not reported.

Variant	Clinical Features	Histological Features	Possible Evolution
Common blue nevus with satellite lesions	A blue-black papule or nodule with a irregular borders, accompanied by guttate blue-black satellite lesions.	Histologic features are that of a common blue nevus.	Not reported. This entity needs to be differentiated from malignant melanoma.
Agminated blue nevus	Multiple blue nevi grouped in a circumscribed area.	Histologic features are that of a common blue nevus.	Not reported.
Atypical (cellular) blue nevus	A patch of blue-greay or blue-brown pigmentation, usually large (> 5 cm) and sometimes ulcerated.	Large, asymmetrical and ulcerated lesions, usually with infiltrative margins; cytologic atypia is usually present (nuclear pleomorphism); there are up to 2/mmq mitotic figures but no atypical mitoses; necrosis is absent.	Atypical histologic features raise the problem of the histologic differential diagnosis with malignant blue nevus/melanoma. There is no consensus among dermatopathologists for the diagnosis of an atypical blue nevus. Some Authors consider it a variant with histologic intermediate features intermediate between a cellular blue nevus and a malignant blue nevus, with uncertain behaviour. Some Authors do not accept the existence of this entity. [7]
Malignant blue nevus / Metastasizing blue nevus	A blue-black nodule or plaque, that may arise within a cellular blue nevus (most often on the scalp), a nevus of Ota, a combined congenital blue nevus or de novo.	Malignant cells of melanocytic origin are observed in the deeper dermis, while epidermal melanocytes are normal. A sheet-like growth pattern is seen. Necrosis, infiltrative borders, nuclear pleomorphism, hyperchromasia and atypical mitotic figures allow a correct diagnosis.	There is debate whether the differences with melanoma are only semantic; some Authors do not accept the existence of this entity, others consider it a malignant variant of a blue nevus. [7]

Case presentation

A 56-year-old Caucasian man was hospitalized in our hospital in May 2012 because of a hemorrhagic cystitis with fever. The patient was affected by severe cognitive impairment, mild blood hypertension, prostatic hypertrophy and had a permanent catheter. During the hospitalization, a dermatologic visit was required because of a large blue lesion on the trunk. On clinical examination, a large mammillated blue plaque involving more than half of the chest wall was observed (Figure 1).

The anamnesis revealed that the patient was born with a large congenital blue nevus that had developed subcutaneous nodules in the last 15 years, slowly increasing in number and size. We formulated the diagnosis of LPTBN-SN.

The relatives of the patient reported on a previous large and deep biopsy, performed almost nine and a half years before in another hospital, which showed the presence of a melanoma on a congenital blue nevus. At that time, due to the dimensions of the lesion and the psychiatric illness of the patient, no treatment was performed. Unexpectedly, no metastases had developed and only a slow increase of the nodules was observed in the following years.

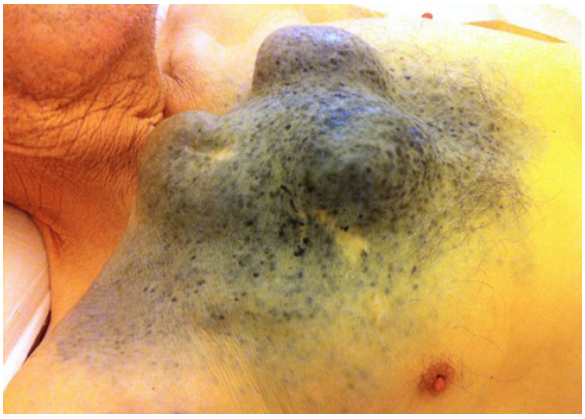

Figure 1. A large mammillated blue plaque involving more than half of the chest wall. Note the surgical scar of the first wide and deep biopsy. [Copyright: ©2015 Savoia et al.]

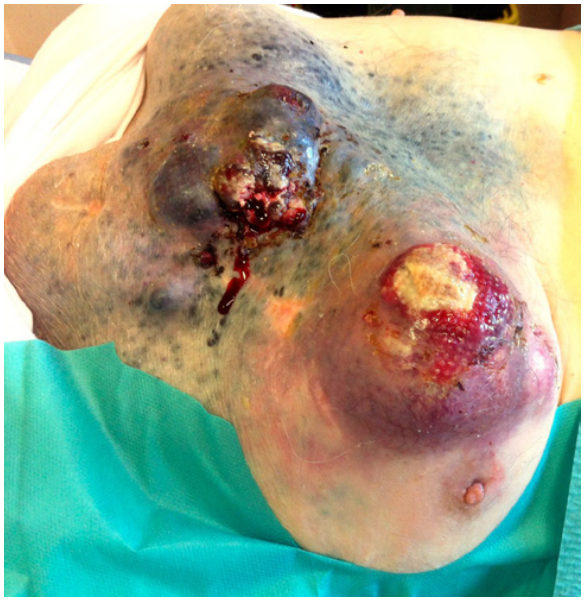

Figure 2. Rapid increase of two of the subcutaneous nodules with ulceration. [Copyright: ©2015 Savoia et al.]

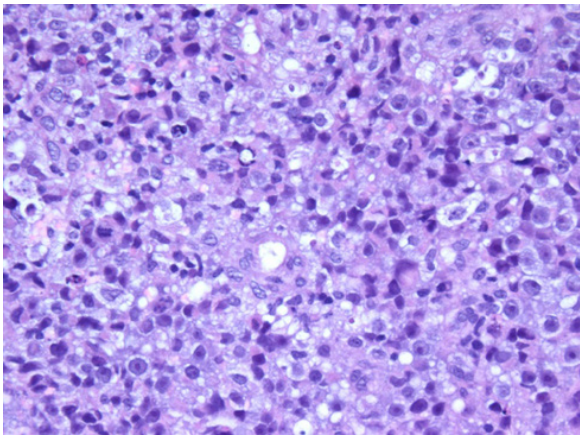

Figure 3. Extremely atypical tumoral cells in the subcutaneous tissue. [Copyright: ©2015 Savoia et al.]

We decided to repeat a skin biopsy of a subcutaneous nodule, and the histopathology was consistent with a benign cellular blue nevus, while the revision of the previous biopsy confirmed the diagnosis of melanoma on a congenital blue nevus.

A strict follow-up of the patient every four months was undertaken, and after one year we observed the rapid increase of two of the subcutaneous nodules with ulceration (Figure 2). A new biopsy was performed, and in this case a histopathologic diagnosis of melanoma was made, confirming the final diagnosis of melanoma arising on an LPTBN-SN (Figure 3).

A total body computer tomography showed lymph node enlargement at the right axilla. Mutation of the BRAF gene was negative. The patient was sent to the palliative care center of our hospital and died three months later.

Conclusions

The term large plaque type blue nevus with subcutaneous cellular nodules was coined in 1999 and refers to a huge blue nevus, usually located on the trunk, that develops subcutaneous nodules many years after the lesion has appeared [8, 9]. Histopathologically, the nodules are characterized by areas resembling common blue nevi and areas resembling cellular blue nevi, with infiltration of subcutaneous and soft tissues, including the fascia and mammary tissues.

The potential malignancy of an LPTBN-SN was discovered only in 2012 [3-6]. Melanoma arising on an LPTBN-SN has a slow local growth and develops local recurrences after surgery or distant metastasis only after many years. In the case reported by Yeh and colleagues in 2012, an interval of 22 years between the diagnosis of melanoma and death due to metastases occurred [5]. This is in contrast with the usually very quick course occurring when a nodular melanoma arises within a congenital nevus. A possible explanation of this strange behavior is the slow accumulation of chromosomal mutations during the years, with a tumoral progression finally leading to an overt aggressive melanoma. However, the absolute and relative risk for developing a melanoma in an LPTBN-SN is still unknown.

There are three peculiar clinical entities that may have a biologic behavior similar to LPTBN-SN: a variant of a nevus of Ota showing a progressive evolution to melanoma with intermediate stages resembling a cellular blue nevus; a giant congenital cellular blue nevus of the scalp; and pigmented neurocristic hamartoma [10-13]. The nodules that develop in the context of such lesions can be regarded as true low-grade melanocytic malignancies that can progress to a higher grade of malignancy over many years. Initially, the lesions can have the trend to grow and infiltrate the surrounding tissues and, if untreated, metastasis and death can occur.

Cutaneous neurocristic hamartoma is the less known entity among the three. It belongs to the group of dermal melanocytic lesions and is characterized by hamartomatous lesions clinically and histologically similar to blue nevi, but with a neural crest-derived Schwann cell component [14].

The case reported here highlights the malignant potential of an LPTBN-SN, the very long course even without treatment and the possible coexistence of benign, borderline or malignant subcutaneous nodules in the same LPTBN-SN.

Patients with large congenital blue nevi should be advised on the potential oncologic transformation of these lesions, the importance of follow-ups should be emphasized and, whenever possible, a preventive complete surgical removal should be evaluated before subcutaneous nodules develop.

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