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Malignant Blue Nevus Arising in a Congenital Cellular Blue Nevus in a Young Woman: Case Report and Review of Literature

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Abstract

Malignant blue nevus is a term related to melanoma arising in association with or that resembles blue nevus. Such lesions are extremely rare with occasional reports and a few small series of cases described in the literature; therefore, the biology and prognosis of such tumors is not well clarified. Due to lack of strictly defined histopathological criteria, such lesions may present a significant diagnostic challenge. We are presenting a case of a malignant blue nevus arising in a congenital cellular blue nevus, presenting as a slowly progressing and asymptomatic pigmented lesion on the buttock of a 21-year-old woman. Histopathological analysis showed presence of a cellular blue nevus as well as features characteristic for malignant blue nevus. The definitive diagnosis was reached only at the histopathological and immunohistochemical examination. The histological features and clinical course in our patient are also discussed in context and the review of the previous related literature.

Keywords: Malignant blue nevus; Melanoma; Congenital cellular blue nevus

Introduction

Malignant Blue Nevi (MBN) or blue nevus-like melanomas are rare melanocytic tumors that may arise in association with or that resemble melanoma, and may have an aggressive course, resulting in metastases and death. Only sporadic case reports and several studies with a few dozen patients with MBN have been described in the literature. Due to the rarity of these tumors, there is still lack of unified histopathological criteria and, the data on the prognosis and outcome of these patients are somewhat controversy. We are presenting a case of a thick and large MBN arising in a congenital cellular blue nevus in a 21-year-old woman, with the review of the previous related literature regarding clinical, dermatoscopical and histopathological features of MBN, as well as biology, genetics and prognosis of these tumors.

Case Report

A 21-year-old woman presented at the Department of Dermatovenereology seeking for medical advice regarding acne form lesions on the face. On examination, the patient also mentioned a slowly growing congenital nevus on her left buttock. Clinically, an unevenly and darkly bluish-grey to black nevoid lesion with irregular borders, measuring up to 15 mm in diameter was observed (Figure 1). Dermatoscopic examination revealed asymmetric, steel blue-gray to black homogeneous pigmentation with whitish veil. Lesion appeared to be consisted of two parts, the major part (measuring around 12 mm) and the adjacent smaller (3 mm in diameter) satellite lesion with subtle fragmented bluish reticular-like formations at the periphery (Figure 2). The patient reported that the satellite pigmentation appeared over the last two years. Patient's medical history and family history were otherwise unremarkable.

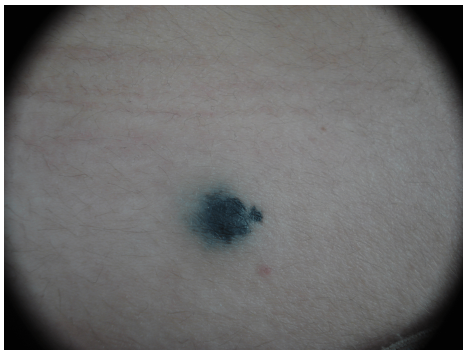

Figure 1: Clinical presentation of a slowly growing congenital nevus the left buttock in a 21-year old woman.

The lesion was excised and biopsy specimen of the tumor was formalin-fixed, paraffin embedded, and sections of 5μ were stained with haematoxylin and eosin. The sections showed a heavily pigmented multinodular melanocytic tumor within dermis and subcutis, measuring up to 2.5 cm in diameter (Figure 3). The tumor exhibited an admixture of pigmented dendritic melanocytes and melanocytes with more abundant, clear cytoplasm. Focally, there were areas of increased cellularity with tumor cells arranged in large fascicles. In these areas, significant cytological atypia and focal epitheloid cell change were also noted (Figure 4). Occasional mitotic activity up to 1 mitosis per mm^2 was identified and there was multifocal tumor necrosis (Figure 5). By immunohistochemistry,

tumor cells expressed S100 and Melan-A strongly and diffusely, as well as HMB-45 focally. The MIB-1 proliferative index was low. Based on these findings, a diagnosis of malignant blue nevus was set, with Clark level V and thickness of at least 15 mm. On primary excision, margins were involved.

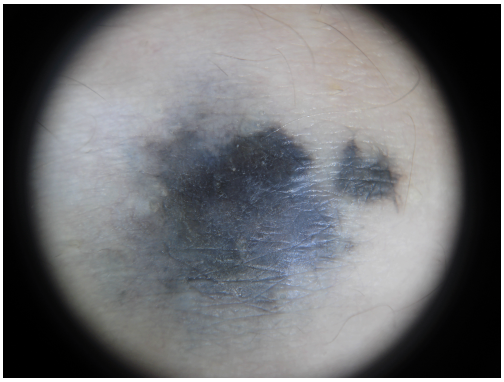

Figure 2: Dermoscopy reveals asymmetric, steel blue-gray to black homogeneous pigmentation with whitish veil. Smaller, satellite lesion displayed sublte fragmented bluish reticular-like formations at the periphery.

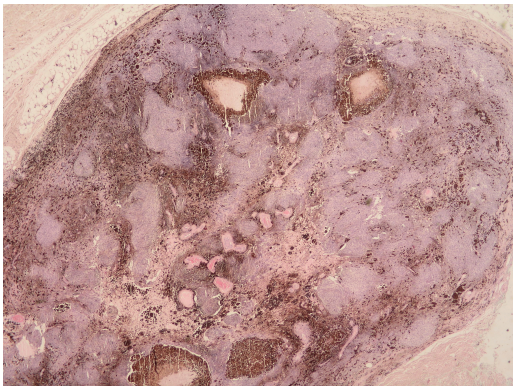

Figure 3: A heavily pigmented multinodular melanocytic tumor (H&E, 2X)

Re-excision of the scar with a 2 cm margin and sentinel lymph node biopsy (in the left inguinal region) were performed and, histopathology of the re-excised specimen as well as sentinel lymph node, showed no evidence of residual tumor or metastases. Routine laboratory studies and PET/CT scan were negative. The patient remained under a regular clinical and imaging follow-up and free of disease 18 months after the excision of primary tumor.

Discussion

Blue nevi are benign lesions characterized by the presence of dermally located pigmented dendritic melanocytes. Clinically, they usually present as a bluish or blue-gray to black colored papule up to 1 cm in diameter, most commonly found on the dorsal sides of the hands and feet or in the head and neck area [1]. The intense blue to gray color of these lesions results from the Tyndall phenomenon, implying the selective absorption of longer wavelengths of light by dermal melanin and the reflection of shorter wavelengths (blue) from the skin [2]. Various subtypes of blue nevi have been described, including common blue nevus, cellular blue nevus, epitheloid blue nevus and deep penetrating nevus [1,3]. Blue nevi are usually stabile over time, however, on rare occasions, malignant melanoma may arise within or in association with these lesions [4]. Therefore, in all cases of blue nevi with changes such as loss of a regular border or the development of satellite lesions, excisional biopsy and histopathological analysis should be performed [5].

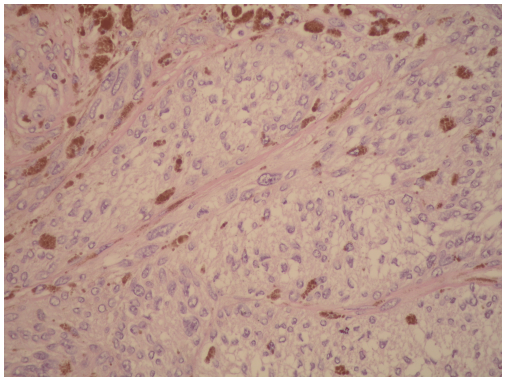

Figure 4: Epithelioid tumor cells with ample cytoplasm and enlarged, atypical nuclei (H&E, 400X)

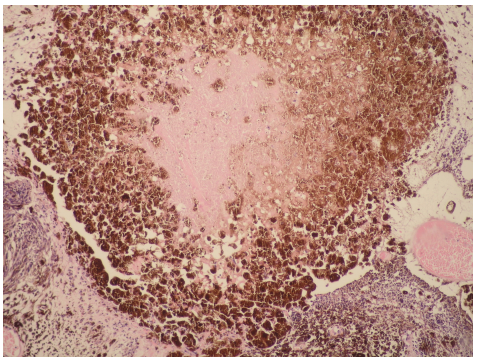

Figure 5: Tumor necrosis masked by melanin pigment (H&E, 200X)

The term Malignant Blue Nevus (MBN) comprises a heterogeneous group of rare malignant melanocytic tumors which are considered to be equally or even more aggressive in behavior than other types of melanoma [6,7]. The term "malignant blue nevus" was first proposed by Allen and Spitz to describe a heterogeneous group of unusual tumors that resembled blue nevi but resulted in metastases and death in some patients [8]. These rare tumors are diagnosed in three different clinicopathological settings. MBN may develop within a cellular blue nevus, which is the most commonly reported scenario. Secondly, MBN may arise in a common blue nevus, which is an extremely rare event [7-10]. Finally, MBN may also present as de novo melanoma that histopathologically displays some features resembling cellular blue nevus [11]. Additionally, sporadic cases in the liteature report that MBN may develop in a giant congenital nevus or in a nevus of Ota [5].

It has been reported that malignant blue nevi commonly develop on the scalp in elderly male population [4,12,13]. Therefore, every bluish newly arising melanocytic lesion on the scalp, especially in elderly men, should be excised [14,15]. According to clinicopathological study conducted by Martin RCW et al., in which 23 MBN were analyzed, the primary tumors were most commonly located on the head and neck area as well as on the trunk (34.8% each), followed by upper limbs (17.4%) and lower limbs (13%) [2]. Cellular blue nevi are commonly located in the the sacrococcygeal and gluteal region and young adults, particularly women, are most commonly affected [4]. Our patient is a young woman with congenital cellular blue nevus in the gluteal region, which underwent a malignant transformation.

Demographic profiles of MBN are still not well established due to its low incidence, small series studied and variations in the definition of the lesion made by different authors. MBN can occur at any age, but is mostly reported in middle-aged adults [4,16]. In the series analyzed by Kachare SD, et al. the average age at presentation was 55.8 years and, in the series reported by Martin RCW, et al. the average age was 44 years [2,16]. It is reported that MBN occurs almost equally frequent in men and women [16], however some studies report higher incidence in male patients [2].

Dermatoscopic appearance of blue nevi commonly shows global pattern as homogeneous mono/dichromatic pigmentation or multichromatic pigmentation. On the other hand, dermatoscopical features of MBN include diffuse whitish-blue veil, round black blotches and a collection of dark colored punctate spots (histopathologically correlating with areas of intense focal necrosis in the papillary and reticular dermis). Under dermatoscope, MBN may also exhibit fragmented bluish reticular-like formations at the periphery (histopathologically corresponding to the presence of free melanin and melanophages in the papillary dermis) [17], as it was the case in our patient. However, on rare occasions benign blue nevi may also display certain "atypical" dermatoscopic features, such as peripheral streaks with branches or satellitosis [18,19]. Therefore, in some cases it is impossible to distinguish between benign blue nevus and MBN with clinical and dermatoscopical evaluation.

In majority of MBN cases the lesions had been present for many years before the excision, and most lesions undergo biopsy because they appear to be an unusual pigmented lesion [4]. Less frequently, these lesions are detected and removed due to rapid growth and ulceration, or due to development of satellite lesion adjacent to previously stable, longstanding lesion [4]. The development of satellite lesion in the blue nevus is an alarming sign of possible malignant transformation. This was also the case in our patients who had blue nevus on the buttock since birth, but noticed the development of satellite pigmentation over the last two years. However, satellitosis has been described in benign blue nevi, although extremely rare [19]. Therefore, differential diagnosis of MBN includes common or cellular blue nevus, atypical cellular blue nevus, primary malignant melanoma, pigment-synthesizing variant of melanoma (so-called animal/equine type) and dermal melanoma metastasis [4].

Histopathologically, both melanomas and MBN may exhibit multiple similar features: cytologic atypia, pleomorphism, increased mitotic activity, abnormal mitotic figures, necrosis, vascular invasion, expansile or destructive growth, and infiltrative margins [4,7,20]. In addition, MBN display the presence of a concomitant or pre-existing blue nevus which, by definition, does not involve epidermis (which is not typical for melanoma) [16]. However, in one of the best documented morphological case studies so far, by Granter SR, et al. (2001), not all of the malignant features were consistently present in adverse outcome cases, with some metastasizing cases lacking features such as necrosis, significant atypical, or the presence of more than 2 mitosis/mm^2. In a study on atypical blue nevi, Barnhill RL et al. have shown a significant lack of interobserver agreement in the diagnosis of atypical blue nevi, thus demonstrating a lack of consensus concerning the acceptable level of atypicality [21]. In the previously mentioned study by Granter SR et al., two major histopathological patterns of MBN were described: one group were tumors that contained a benign component and easily detectable malignant features of expansile asymmetric nodule which was recognizable at low power, including a sheet-like growth pattern with loss of normal biphasic or alevolar architecture (which is seen in cellular blue nevus), as well as variable parts of necrosis. Another group of tumors had no associated benign nevus component. These tumors were more difficult to diagnose because at low power, they mimic the growth pattern of a benign blue nevus. Under closer inspection, one may observe architectural and cytomorphological features of malignant lesion, such as infiltrative borders, frequent mitoses, necrosis, nuclear pleomorphism and hyperchromasia, and epitheloid cell morphology [4].

Some authors imply that "malignant blue nevus" is only a decriptive term and, that the histopathological entity decribed by this term is actually a melanoma, therefore suggesting the use of term "blue nevus-like melanoma" [2].

An interesting and rare phenomenon of blue nevi involving lymph node has been described in the literature [2]. In such cases, blue nevus cells are found in the lymph node capsule or within the intranodal fibrous trabeculae, in contrast to involvement of lymph node by metastatic MBN or melanoma where usually subcapsular sinus region is involved with the disturbed architecture of the lymph node due to the expansile tumor mass [2]. This distribution pattern of nevus cells represents a very useful diagnostic feature that may help avoid over diagnosis of sentinel lymph node metastasis.

It is well documented that approximately 50% of cutaneous melanomas exhibit BRAF mutations and 15-20% exhibit NRAS mutations [22]. Targeted therapy for patients with advanced melanoma has been advancing with agents directed to specific mutations in tumor, in particular BRAF and NRAS mutations [22]. However, a subset of melanoytic tumors does not exhibit the BRAF and NRAS mutations. This group of tumors includes uveal melanoma (which arises from the choroidal cells of the eye and has different biology from cutaneous melanoma) and intradermal melanocytic proliferations, such as blue nevi, nevus of Ota and Ito, mongolian spot and MBN [23]. Van Raamsdonk CD, et al. found that the majority of blue nevi (83%, N=29) and half of uveal melanomas (46%, N=48) exhibit somatic mutations in the heterotrimeric G protein alpha-subunit, GNAQ. The same mutation was found in 50% of MBN, however the study included a small number of MBN (N=4). The mutations occur exclusively in codon 209 in the Ras-like domain and result in constitutive activation, turning GNAQ into a dominant acting oncogene, indicating that there is an alternative route to MAP kinase activation in melanocytic neoplasia [23]. These findings might provide new opportunities for future therapeutic intervention in patients with MBN.

The data on the prognosis for patients with MBN in the literature are somewhat controversial. Some authors proposed that MBN is a "low grade malignancy" [7]. Other reports and case studies suggested that MBN are more aggressive than other melanomas [6]. However, in one of the recent study analysis of 23 MBN cases, no difference in survival or in the risk of lymph node or distant metastases was

observed between patients with MBN and a matched control group of melanoma patients, after a median follow-up of 36.5 months [2]. MBN are diagnosed generally with greater tumor thickness then other types of melanoma, but this does not seem to reflect in higher propensity to lymph node metastases or in decreased survival [2,16]. Additionally, the latest and the largest study on MBN to date, which included 52 patients with MBN, demonstrated similar clinical behavior and survival between patients with MBN and those with melanoma, even though MBN were more likely to present with metastatic disease then melanomas (15.2% vs. 4%, P=0.0028) [16]. On the other hand, both groups (MBN and melanomas) had similar age of presentation (55.8 vs. 55.7, respectively, P=0.527), gender distribution (male 50% vs. 55%, P=0.44), and nodal positivity rate (9.6% vs. 5.4%, P=0.22) [16].

The highest risk for the development of metastases is in the first two years [2], but there have been reports on metastases from MBN occurring 15 years after the removal of the primary tumor [21]. In a series of 10 patients with MBN studied by Granter SR, et al., clinical follow-up showed evidence of recurrence or metastases in all seven cases for which the data was available [4]. Of these 7 patients, recurrence occurred in 3 of them, whereas metastases developed 4 patients, involving lungs (3 patients), liver (2 patients), lymph nodes (one patient), and bone (one patient). Three patients with metastases died, and four of the patients with metastasis were still alive at the time of the publication [4]. According to the data described above, it seems that MBN represent a highly aggressive variant of melanoma.

Conclusion

Malignant blue nevi are extremely rare tumors that may clinically and histopathologically resemble blue nevi, but may have an aggressive course, resulting in metastases and fatal outcome. Many cellular blue nevi cases remain challenging and difficult to classify as benign or malignant, because lesions showing overt malignant characteristics are exceptionally rare. Some of the attributes that are helpful in discriminating melanomas from nevi in the conventional setting, such as size, presence of mitoses, necrosis, hypercellularity, cytologic atypia, and regional lymph node involvement seem to lack true specificity in the differential diagnosis of cellular blue nevi vs. MBN. Consequently, at the current moment there is a significant lack of interobserver agreement in the diagnosis of atypical cellular blue nevi and malignant blue nevi [21]. In the absence of well-studied molecular prognostic markers, which may occur in the future, a careful histopathological evaluation of the entire lesion with multiple sections remains the mainstay of diagnosis. In lieu of strictly defined limits of acceptable atypicality, the final diagnosis will require a balanced; overall assessment of the lesion, including all of the above described attributes. Our patient is a young woman, diagnosed with an advanced MBN in terms of primary tumor thickness (15 mm) and tumor size (2.5 cm in diameter) arising within congenital nevus over the buttock region. There are only sporadic reports on MBN arising in congenital nevus, and this is one of the largest and one of the thickest MBN reported. However, sentinel lymph node in our patient was negative and, the patient remained under regular clinical and imaging follow-up, free of disease 18 months after the removal of the primary tumor. In conclusion, it seems that MBN represents a variant of melanoma, with certain particularities in terms of clinical and histopathological characteristics, and should therefore be treated according to the same guidelines as that of melanoma.

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