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Primary malignant melanoma with pseudovascular morphology: a diagnostic pitfall

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Abstract

Melanoma is a neoplasm with a heterogeneous clinical presentation and several histopathological variants have been described. Although histopathological evaluation remains the diagnostic gold standard, unusual morphology of some melanomas can lead to pathologic misinterpretation, as they can be confused with other non-melanocytic tumors. Here, we present a case of nodular melanoma with pseudovascular morphology characterized by uncommon empty branching slit-like spaces, reminiscent of rete testis vessels, for which we suggest the name of retiform melanoma to distinguish it from angiomatoid melanoma. Immunohistochemical analysis and ancillary molecular tests helped us characterizing this neoplasm, underscoring the need for clinical-morphological-molecular correlation for the correct diagnosis of unusual cases.

Key words: diagnostic pitfall; immunohistochemistry; malignant melanoma; next-generation sequencing; pseudovascular morphology.

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Introduction

Melanoma is a neoplasm with a heterogeneous clinical presentation showing different histopathologic patterns, some of which are uncommon and unusual, with consequent problems in recognition and a high risk of misdiagnosis.[1,2] Although the histopathological evaluation still remains the diagnostic gold standard, microscopic features of some rare variants can lead to erroneous pathologic diagnosis, as they can be confused with other non-melanocytic tumors.[3] Thus, immunohistochemistry has a primary role in revealing the differentiation of the neoplastic cells to achieve the correct diagnosis, which is crucial for the subsequent patients' management. The introduction of genetic analysis may contribute to the aim, as a specific molecular profile may be associated with tumors that share similar morphological features.[4] Here, we present a case of nodular melanoma with pseudovascular morphology characterized by uncommon empty branching slit-like spaces, reminiscent of rete testis vessels, for which the name of retiform melanoma could be suggested, showing *NRAS* mutation on next-generation sequencing (NGS) analysis.

Case Report

A 72-year-old Caucasian man referred to the Dermatology Clinic for an ulcerated polypoid lesion of the right calf (Figure 1), which was immediately excised and sent for histopathological examination. Microscopically, it resulted in a nodular neoplasm, delimited by an epidermal collaret, constituted by medium-sized epithelioid cells arranged in a solid growth pattern (Figure 2a). The lesion was limited to the dermis, without any evident epidermal component. In the superficial aspect, neoplastic cells showed a hobnail appearance, delimiting empty branching slit-like spaces, resembling rete testis vessels (Figure 2 b-d). The neoplastic elements showed severe cytological atypia and pleomorphism, high mitotic activity, including atypical figures, and single cell necrosis (Figure 2 e,f). The branching slit-like spaces were strongly evocative of a vascular tumor, with epithelioid cytology and retiform growth pattern, even though they were empty and not filled with erythrocytes, as is commonly seen in vascular neoplasms. No melanin pigment was found. Thus, immunohistochemical analysis was necessary to establish the origin of the neoplasm. Diffuse positivity for melanocytic markers S100 and Melan-A was detected (Figure 3 a,b), while cytokeratin AE1/AE3 and vascular markers (CD34, CD31, D2-40, ERG, and FLI1) were entirely negative (Figure 3 c,d). Based on the morphological and immunohistochemical features, a diagnosis of ulcerated nodular melanoma, with pseudovascular spaces, widely invading the dermis, with a Breslow thickness of 12 mm, was proposed. Ancillary molecular tests were performed and NGS analysis revealed *NRAS* Q61R (c.182A>G) mutation, with a variant allele frequency (VAF) of 30%. Other mutations with >5% VAF were not detected (*Supplementary Material*).

Discussion

The case we reported shows rare and unusual morphological features of nodular melanoma, as it presents characteristic empty branching pseudovascular spaces reminiscent of rete testis, resem-

bling an epithelioid angiosarcoma or retiform hemangioendothelioma. The presence of those slit-like empty clefts differs this entity from the rare variant of angiomatoid melanoma, which is characterized by variably large spaces filled with erythrocytes.[5,6] On the other hand, it does not represent a case of transcriptional reprogramming with angiogenetic network activation, previously described in advanced malignant melanoma.[7,8] In our opinion, this case represents more likely a morphological variant than a true reprogramming of transcription factor, as by immunohistochemistry only melanocytic markers (S-100 and Melan-A) were expressed, while the vascular ones (CD34, CD31, D2-40, ERG, and FLI1) were completely negative. Furthermore, ancillary tests may be helpful in excluding the suspicion of vascular invasion by melanoma cells, as these clefts are lined by melanocytes and not by endothelial cells. Branching empty spaces resembling hematic or lymphatic vessels are frequently observed in benign melanocytic nevi with a prominent dermal component.[9] It is generally accepted that this feature is attributable to tissue processing artefacts. In our case, as the lesion is large and presents many apoptotic and necrotic melanocytes, it is possible to speculate that this peculiar morphological feature may be induced by loss of intercellular adhesion between tumor cells or central necrosis of neoplastic nodules. The presence of intraepidermal melanoma component, whenever present, represents a helpful clue for the diagnosis.

Although histopathologic evaluation remains the mainstay approach to melanoma, the introduction of genetic analysis, in addition to immunohistochemical stainings, may contribute to the correct diagnosis and classification of lesions that may share similar morphological features, considering that melanocytic tumors show different genetic profiles from vascular ones. About 70% of melanomas show pathogenic variants in *BRAF* or *NRAS* genes,[10,11] while angiosarcoma most frequently harbors alterations in *MYC*, *TP53*, *KDR*, *FLT4*, and *CRKL* genes,[12] and epithelioid hemangioendothelioma fusions of *WWTR1-CAMTA1* or *YAP1-TFE3*

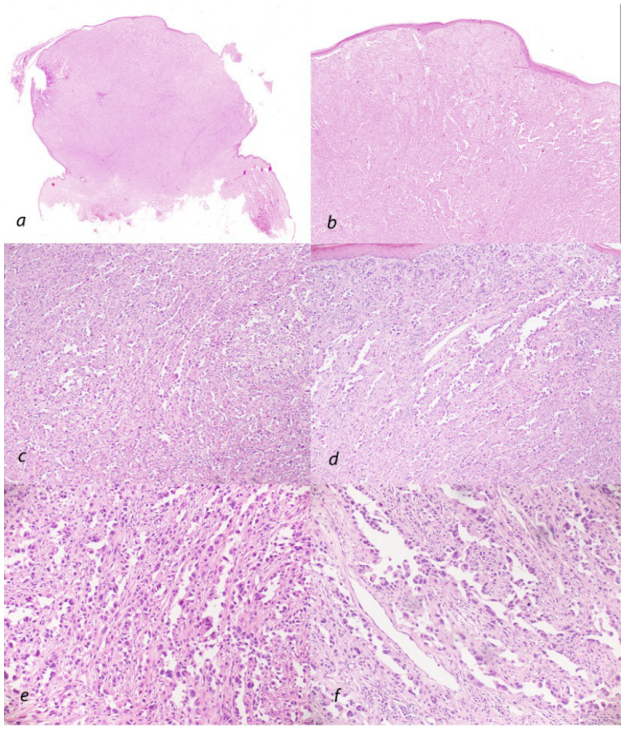


Figure 2. Histopathological pictures: nodular melanoma with retiform pseudovascular morphology. **a**) Nodular neoplasm delimited by an epidermal collaret (hematoxylin-eosin, original magnification: 10×). **b-d**) branching slit-like spaces reminiscent of vascular neoplasms in the superficial aspect of the tumor (hematoxylin-eosin, original magnification: b) 40×; **c-d)** 100×). **e-f**) Details of the neoplastic cells arranged to delimitate the pseudovascular spaces (hematoxylin-eosin, original magnification: 200×).



Figure 1. Clinical picture: angiomatoid ulcerated polipoid lesion of the right calf mimicking a vascular neoplasm.

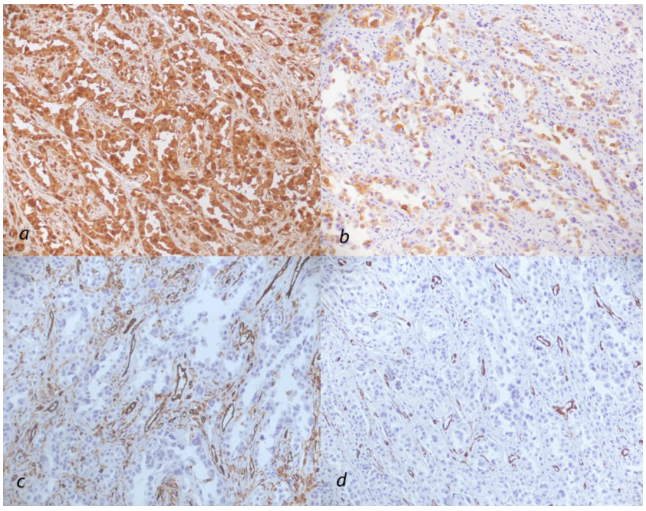


Figure 3. Immunohistochemical stainings. **a**) S100; **b**) Melan-A; **c**) CD34; **d**) CD31 (original magnification: 200x).

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genes.[13] Molecular analysis by NGS, in our case, revealed the *NRAS* Q61R mutation. Pathogenic variants of *NRAS* are reported in 20% of all melanomas[14] and are more prevalent in lesions arising on the skin of the limbs, showing nodular histotype. They confer a more aggressive behavior to the neoplasm, compared to *BRAF*-mutant or wild-type disease, since patients with a *NRAS*-mutant melanoma have a worse prognosis with significantly shorter median overall survival. In 80% of cases, *NRAS* pathogenic variants occur at codon 61 and most frequently involve a glutamine to arginine/lysine/leucine substitution (Q61R/K/L). These mutations block *NRAS* into a GTP-bound state, impairing its GTPase activity[4,15] and favoring neoplastic cells' proliferation and survival.

In our case, the identification of an *NRAS* mutation supported the immunohistochemical findings and confirmed the diagnosis of melanoma, as mutations in this gene are not reported in angiosarcoma or hemangioendothelioma. To date, the same *NRAS* Q61R pathogenic variant has been reported only in a case of angiosarcomatous transdifferentiation of metastatic melanoma.[16] In that case, the primary cutaneous melanoma had no signs of heterologous differentiation, while the metastatic lymph nodes presented two different patterns. The first one was solid, positive for melanocytic markers and negative for vascular ones, while the latter was constituted by vascular spaces lined by highly atypical cells positive for endothelial markers and negative for those melanocytic. A diagnosis of divergent differentiation, instead of a collision tumor, was formulated by the authors based on molecular analyses, which showed the same *NRAS* Q61R mutation in both populations.[16]

Conclusions

The case described here shows a peculiar pseudovascular morphology resembling rete testis vessels, for which the term retiform melanoma could be suggested. Recognition and characterization of this rare form of melanoma are useful to prevent misdiagnosis. In this context, combining the clinical and histopathological pictures together with immunohistochemical and genomic analyses may be helpful to make the correct diagnosis, with implications for patients' clinical management.

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Online Supplementary Material:
Description of the analytical procedures and the gene panel used in the molecular analysis of this case of melanoma, with pseudovascular morphology.

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Conflict of interest: the authors have no conflict of interest to declare. CC is Editor-in-Chief of *Dermatology Reports.*

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Consent for publication: the patient gave his written consent to use his personal data for the publication of this case report and any accompanying images.

Availability of data and materials: all data underlying the findings are fully available.

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