Malignant peripheral nerve sheath tumour-like primary cutaneous malignant melanoma

J Cruz, J S Reis-Filho, J M Lopes

Malignant melanoma is known for its protean cytomorphological features, architectural patterns, and stromal changes, in addition to its ability to mimic various benign and malignant non-melanocytic tumours. Anecdotal cases of metastatic malignant melanoma simulating soft tissue sarcomas have been reported. Interestingly, this mimicry is more often seen in recurrent lesions and metastatic deposits. This report describes a case of a primary spindle cell cutaneous malignant melanoma with a prominent neural-like fascicular pattern and nuclear palisading, simulating a conventional malignant peripheral nerve sheath tumour (MPNST). Clinical, microscopic, and immunohistochemical features of the different entities included in the differential diagnosis of cutaneous spindle cell malignant tumours, such as MPNST, atypical fibroxanthoma, and spindle cell squamous cell carcinoma are discussed. Of note, the presence of an atypical epidermal or junctional component, cell pigmentation, and cell nesting, in addition to diffuse and strong reactivity for S-100 protein and other melanocytic markers, are helpful in the diagnosis of these troublesome lesions.

A 54 year old man presented with an ulcerated, infiltrative, hyperpigmented, slightly raised lesion in the plantar surface of the right foot. On physical examination, no other lesions were detected and no café au lait spots or other stigmata of neurofibromatosis 1 (NF1) were seen. A wide local excision with clear margins was performed. The patient remains free of disease 168 months after diagnosis.

PATHOLOGICAL FINDINGS

The specimen consisted of a 35 × 30 × 20 mm skin ellipse with a centrally located, partially ulcerated, pigmented nodular lesion, with irregular borders and colour variegation, measuring 28 × 20 × 10 mm. Microscopically, a vaguely lobulated, highly cellular, asymmetric lesion extended from the epidermis into the subcutaneous tissue. The dermal component of the tumour comprised pleomorphic, malignant appearing, spindle shaped cells containing hyperchromatic, elongated nuclei with clumped chromatin and moderately abundant, faintly eosinophilic cytoplasm arranged in fascicles or nerve-like whorls, with little intervening stroma (fig 1A). Areas with a remarkable nuclear palisading were disclosed (fig 1B). Neoplastic cells sometimes had a perivascular distribution (fig 1B), which occasionally gave the impression that they were “herniating” into the vessel lumen. Cells with nuclear pseudoinclusions (fig 1C) and bizarre multinucleated neoplastic cells were also observed. In the superficial dermis, plump spindle shaped neoplastic cells arranged in nests were occasionally seen (fig 1C). At the edge of the lesion, an inconspicuous, asymmetric junctional component was found (fig 1D). Rare cells with dusty Masson-Fontana positive granules were also present. Definitive lymphovascular spread was seen at the tumour periphery. Tumour infiltrating lymphocytes were classified as non-brisk, and no areas of necrosis, satellite nodules, or regression were seen. The tumour was 8.5 mm thick and classified as Clark level V. The mitotic index was 1.2/10 high power fields (0.79/mm²).

Immunohistochemistry with antibodies for vimentin, S100 protein, gp100 (HMB-45), CD34, and cytokeratins (MNF116 and CAM 5.2) was performed. A strong and diffuse reactivity of the neoplastic cells (> 90%) for vimentin, S-100 protein (fig 1E), and gp100 (HMB-45) was observed. All other markers were negative.

DISCUSSION

Cutaneous malignant melanoma (MM) is known for the plethora of morphological appearances it can assume. Several histopathological patterns have been reported, including fasciulation, whorling, swirling, nesting, trabeculation, pseudorosetting, desmoplastic/neurotropic, pleomorphic (atypical fibroxanthoma-like), haemangioepithelial, myxoid, adenoid/pseudopapillary, and naevoid.

MMs can also contain large pleomorphic cells, small cells, signet ring cells, balloon cells, lipoblast-like, and plasmacytoid cells. Occasionally, differentiation towards non-melanocytic structures can be seen.

In addition, MM can mimic several benign and malignant non-melanocytic tumours, including poorly differentiated carcinomas, neuroendocrine tumours (Merkel cell carcinoma), lymphomas (particularly anaplastic large cell lymphoma), germ cell tumours, and different types of soft tissue sarcomas.

“Cutaneous malignant melanoma is known for the plethora of morphological appearances it can assume”

Several cases of metastatic MM simulating sarcomas are on record, including cases of MM mimicking monophasic synovial sarcoma, fibrosarcoma, malignant fibrous histiocytoma, dermatofibrosarcoma protuberans, leiomyosarcoma, liposarcoma, embryonal rhabdomyosarcoma, haemangioepithelioma, primitive neuroectodermal tumour, and malignant peripheral nerve sheath tumour (MPNST). Interestingly, these misleading patterns are more often seen in recurrences and in metastatic deposits than in primary lesions.

In the most comprehensive study of metastatic MM mimicking MPNST, King et al described the morphological overlaps between these lesions and true MPNSTs. These authors reported 16 cases of metastatic MM with histopathological features simulating conventional MPNST; only one of six

Abbreviations: AFX, atypical fibroxanthoma; MITF, microphthalmia associated transcription factor; MM, malignant melanoma; MPNST, malignant peripheral nerve sheath tumour; NF1, neurofibromatosis 1
cases with a known primary tumour had a predominantly fusiform cell population. All tumours were positive for vimentin and showed heterogeneous reactivity for S-100 protein and HMB-45 (14 of 16 cases had a strong and diffuse immunoreactivity for S-100 protein and five of 15 cases were positive for HMB-45). These authors also advanced a list of clinicopathological features that may serve as guidelines for the diagnosis of MM mimicking MPNST. Briefly, pathologists should entertain the diagnosis of metastatic MM when one or more of the following are seen in a spindle cell neoplasm: (1) tumour localised within or close to a lymph node; (2) absence of continuity with a major nerve or a neurofibroma, or absence of neurofibromatosis; (3) presence, or history of past primary MM; (4) strong and diffuse S-100 protein immunoreactivity (S-100 protein is usually focal and/or weak in MPNSTs); and (5) immunoreactivity for other melanoma markers (HMB-45, microphthalmia associated transcription factor (MITF), tyrosinase, and melan A). To the best of our knowledge, four cases of primary cutaneous MM mimicking MPNST have been described to date. Our present case illustrates another spindle cell primary MM with a prominent neural-like fascicular pattern and nuclear palisading, strikingly mimicking a conventional MPNST.

MPNST is a tumour of adults, with the peak incidence in the 3rd to 6th decades. Approximately two thirds of the cases arise from neurofibromas, more frequently of the plexiform type, and in the clinical setting of NF1. MPNSTs may occur almost anywhere in the body, although they most commonly affect the buttocks, thigh, brachial plexus, upper arm, and paraspinal region. Cutaneous MPNSTs are exceedingly rare.

**Take home messages**

- We report a case of a primary spindle cell cutaneous malignant melanoma with a prominent neural-like fascicular pattern and nuclear palisading, simulating a conventional malignant peripheral nerve sheath tumour.
- The presence of an atypical epidermal or junctional component, cell pigmentation, and cell nesting, in addition to diffuse and strong reactivity for S-100 protein and other melanocytic markers, are helpful in the differential diagnosis of these troublesome lesions.
and almost always restricted to patients with NF1. In our case, NF1 (von Recklinghausen’s disease) was excluded. Subtle but useful histological features to recognise the melanocytic origin of the neoplasm are the presence of an epidermal or junctional component, which may be quite inconspicuous, cell pigmentation, and nesting. Immunohistochemistry plays a major role in the differential diagnosis of MM and MPNST. Although S-100 protein is usually positive in both, its distribution is diagnostically important: whereas MMs are diffusely and strongly positive for S-100 protein, MPNSTs are only focally positive for this marker. Other melanocytic markers, such as gp100 (HMB45), tyrosinase, NKI-C3, MART1 (melan A), and MITF, also help to differentiate these two tumours. It should be noted that their sensitivity is relatively low for spindle/desmoplastic MMs. 

The differential diagnosis of spindle cell cutaneous MM also encompasses other lesions, including atypical fibroxanthoma (AFX) and spindle cell squamous cell carcinoma. AFX is a benign lesion, which usually affects the head and neck region of the elderly, especially men. Histopathologically, it is characterised by a dermal nodule composed of bizarre cells arranged in a haphazard to fascicular pattern. These cells are spindle shaped or rounded, pleomorphic, and with numerous atypical mitotic figures. Pigmentation, secondary to the ability of the neoplastic cells to phagocytose and degrade erythrocytes, with the accumulation of haemosiderin in their cytoplasm, is not uncommon. Differentiation from MM may be achieved by the lack of in situ melanoma in the overlying epidermis and the absence of Masson-Fontana positive, iron negative melanin pigment. Moreover, AFXs are usually positive for vimentin, CD68, muscle specific actin, and α smooth muscle actin, and negative for S-100 protein and other melanocytic markers. Spindle cell squamous carcinomas may also be entertained in the differential diagnosis of MPNST-like MM; however, these tumours characteristically occur in sun damaged skin areas, are positive for epithelial markers (mainly high molecular weight cytokeratins), and are negative for S-100 protein and other melanocytic markers. Moreover, keratinocytic atypia and/or Bowen’s disease may be found at the edges of the main lesion.

“Immunohistochemistry plays a major role in the differential diagnosis of malignant melanoma and malignant peripheral nerve sheath tumour”

In conclusion, in small skin biopsies or in ulcerated cutaneous lesions, without appropriate epidermal representation, and particularly in metastases of unknown primary tumours, pathologists must bear in mind that MM can present with peculiar histopathological patterns, which can simulate various non-melanocytic neoplasms. For primary lesions, a diligent search for intra-epidermal pagetoid spread, dermo-epidermal junctional activity, cell nesting, and pigmentation, in addition to an appropriate immunohistochemical panel, are required for the proper diagnosis of these remarkably troublesome lesions.

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