

Case Report

Cutaneous Epithelioid Malignant Peripheral Nerve Sheath Tumor: A Case Report

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Malignant peripheral nerve sheath tumor (MPNST) is a rare soft tissue sarcoma arising from neuroectoderm-derived cells comprising the outer coverings of peripheral nerves. Given the diverse cell types comprising the peripheral nerve sheath, both benign and malignant nerve sheath tumors display a wide range of histologic appearances. MPNST can arise either in association with proximal nerve trunks at deep body sites, or from distal nerve branches residing within skin and subcutaneous tissues. Overall, roughly 50% of MPNST arise in patients with neurofibromatosis type I. The remainder occur sporadically. We report herein a rare epithelioid example of MPNST arising sporadically within a cutaneous neurofibroma. We also offer a brief clinico-pathologic review of MPNST, including diagnostic workup, differential interpretation, treatment and prognosis.

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INTRODUCTION

The peripheral nerve sheath is formed by a morphologically distinct group of cells, include Schwann cells, fibroblasts, and perineurial cells. One such lineage may predominate within a peripheral nerve sheath neoplasm, as in schwannoma and perineuroma, or more than one lineage may overgrow, as in neurofibroma. Benign nerve sheath tumors are common, especially within superficial soft tissues and skin. Malignant tumors, in contrast, are much rarer and arise most commonly from larger nerve trunks at deeper sites. Malignant peripheral nerve sheath tumors (MPNST) show a much higher relative incidence in neurofibromatosis patients. Still, roughly half of all MPNST cases arise sporadically.¹

A wide range of histo-morphologic appearances has been reported in MPNST.² This range encompasses differentiation along non-neural cell lines, including adipose, bone, and skeletal muscle (the lattermost referred to as Triton tumor). Most commonly, MPNST consist of spindle cells growing in fascicles. At their periphery, these spindle cells display varying degrees of infiltrative growth. Higher grade examples of MPNST may lose their "neuroid" appearance and resemble malignant solitary fibrous tumor, synovial sarcoma, or even "small blue cell" tumors. Uncommonly, MPNST display epithelioid features: being composed either focally or diffusely of polyhedral rather than spindly cells. These rare cases may mimic other spindle-and-epithelioid-cell neoplasms,

including sarcomatoid carcinoma, other epithelioid true sarcomas, and malignant melanoma. In this report, we describe an epithelioid example of MPNST arising sporadically within a cutaneous neurofibroma.

CASE REPORT

A 47-year-old Caucasian male, having no significant medical history, presented to dermatology clinic with a long-standing nodule on his right lateral trunk. The patient stated that he believed the nodule had been slowly increasing in size. Clinical examination confirmed the presence of a 2 cm diameter, non-tender, mobile but firm, subcutaneous nodule. No other cutaneous or superficial soft tissue abnormalities were evident. The preoperative clinical impression was one of a benign cyst. The patient was referred for simple excision. Gross pathologic examination of the excised specimen revealed a firm, 2 cm diameter, solid nodule having a homogeneous, yellow-white, cut surface. Histopathologic examination (**Figure 1**) demonstrated a cellular proliferation composed of epithelioid cells showing nuclear enlargement, nuclear pleomorphism, and rare mitotic figures. In other areas of the lesion, its constituent cells were smaller and more bland, and were embedded within a loose fibromyxoid stroma. Immunohistochemical stains (**Figure 2**) revealed both cell populations to be diffusely positive for S-100 protein and for SOX10, but negative for MART-1 and MiTF. Pancytokeratin and desmin immunostains were also entirely negative. EMA immunostaining highlighted only benign perineurial cells surrounding small nerves trapped within the tumor. The proliferation marker, Ki-67, revealed a markedly increased proliferative index within the epithelioid component only

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(approximately 10% of such cells). An immunostain for INI-1, performed at another institution, demonstrated positive (i.e. normal/retained) nuclear staining within tumor cells.

Taken together, the morphologic and immunohistochemical features of this tumor established a diagnosis of malignant

peripheral nerve sheath tumor, of epithelioid cell-type, of low grade, arising in association with a neurofibroma. Re-excision to establish clear margins was recommended. Examination of the follow-up excision specimen revealed no residual neoplasm. The patient is currently well, showing no signs of local recurrence or metastasis.

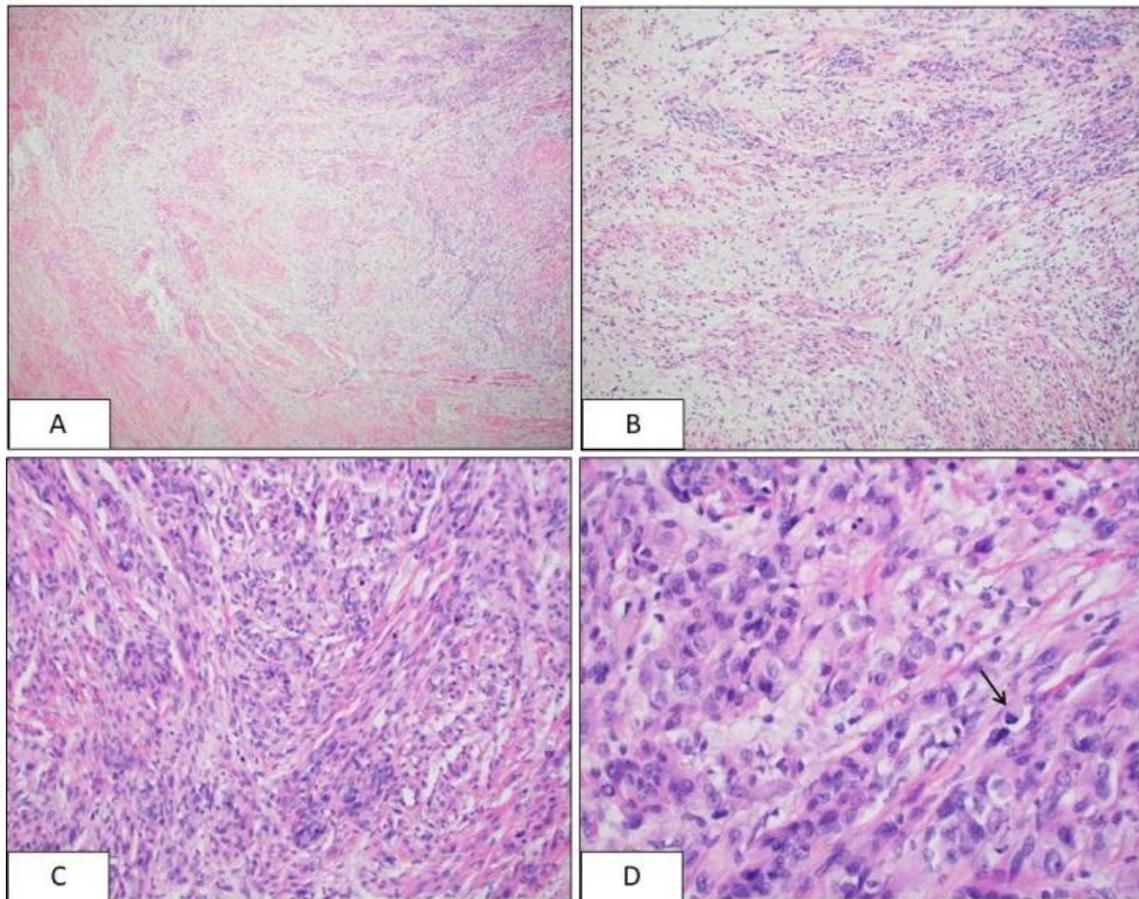


Figure 1. Hematoxylin and eosin stain sections. **A & B:** Low-power views showing pale staining areas of small cells within a loose stroma consistent with neurofibroma (lower left portion of the fields). Darker staining more cellular areas are seen in the upper right corners consisting of atypical spindled and epithelioid cells (4X & 10X). **C & D:** High-power views of the more cellular areas showing dense collections of atypical epithelioid and spindled cells. Notable nuclear pleomorphism and mitotic figure (arrow) are evident (20X & 40X).

DISCUSSION

We report herein a case of epithelioid-variant malignant peripheral nerve sheath tumor (eMPNST) arising within the subcutaneous tissue of a patient lacking other clinical features of neurofibromatosis. Cases like this are rare: MPNST (of all subtypes) comprise only 5-10% of soft tissue sarcomas;³ epithelioid variants have been reported to comprise less than 5% of those; and fewer than 10% of MPNST arise within skin or superficial subcutaneous tissues.³ Roughly half of all MPNST cases arise in patients having neurofibromatosis type I (NF1).¹ In such patients, a roughly 10% lifetime-risk of developing MPNST has been reported.¹ Another 10-20% of MPNST cases have been attributed to prior ionizing radiation

exposure; the remainder are idiopathic.³ The median age of first occurrence for MPNST is 35 years, with NF1 patients presenting slightly earlier.²

The overall rarity of cutaneous MPNST, combined with an unusual epithelioid appearance, complicates correct identification. The presence of polyhedral cells having ample cytoplasm, rather than the more typical fascicular growth of spindle cells, warrants consideration of both primary and metastatic, poorly differentiated carcinoma. In our case, carcinoma was excluded, in part, by negative immunostaining for the epithelial markers, pancytokeratin and EMA.

Differentiation of epithelioid MPNST from melanoma is more challenging given the similarity of their immunostaining profiles. Melanoma and eMPNST both arise from neural crest-derived cells; both show strong immunostaining for S-100 and SOX10.⁴ Definitive exclusion of melanoma may thus require applying more specific markers of melanocytic differentiation. In our case, we demonstrated negativity for the

melanosomal marker, MART-1, and for the melanocytic transcription factor, MiTF. A final note regarding S100 immunostaining in MPNST: although strong and diffuse S100 protein positivity is seen in most eMPNST, only 50-90% of conventional, spindle cell MPNST show positive S100 staining. In many conventional cases, only patchy, weak S100 positivity is demonstrated.^{2,5}

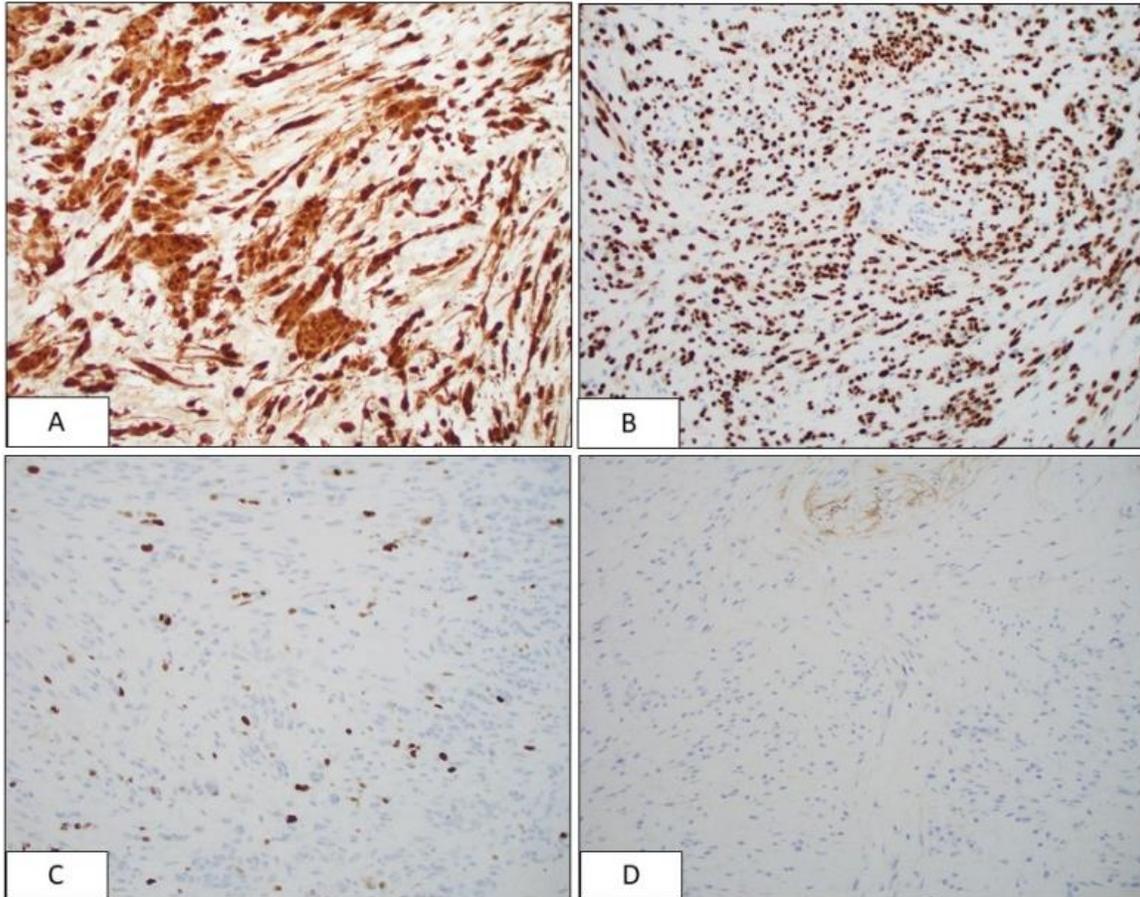


Figure 2. Immunohistochemical stained sections. **A:** Strong diffuse nuclear and cytoplasmic staining for S-100 protein in tumor cells. **B:** Strong nuclear staining for SOX10 in tumor cells (a blood vessel in the center of the field is negative). **C:** The proliferation marker Ki-67 highlights approximately 5% of tumor cells. **D:** Tumor cells are negative for EMA (benign perineural cells are positive in the top center of the field).

Less common entities within the differential interpretation of superficial sarcomas having epithelioid features include epithelioid sarcoma and the epithelioid-variant of synovial sarcoma. In our case, negative immunostains for pancytokeratin and EMA militate against both entities.⁶ Moreover, immunostaining for INI1/SNF5 was retained in our case, largely excluding the former entity. A note of caution regarding INI1: nuclear labelling is retained in only about half of eMPNST cases.⁷ For this reason, other immunohistochemical markers should be employed when distinguishing eMPNST from epithelioid sarcoma.

It should be emphasized that histopathologic recognition of MPNST relies on a combination of immunohistochemical and

histopathologic features. One such feature -- one that greatly aided in our workup and diagnosis of the current case - is identification of a precursor, benign nerve sheath neoplasm (i.e. neurofibroma, and less commonly, schwannoma). Thorough tumor sampling (i.e. complete submission of smaller masses, and not less than 1 cassette per cm of overall tumor diameter for larger masses), followed by careful evaluation of H&E-stained sections, may thus yield the most helpful information regarding nerve sheath origin. In our case, the intimacy of the tumor's epithelioid component with a clearly benign neurofibroma, and the presence within that component of cytologic atypia and mitotic figures, took us most of the way to our eventual diagnosis of eMPNST - that despite its small size, superficial location, and lack of necrosis. Although no

widely agreed-upon grading system for MPNST currently exists, most reports site the overall degree of differentiation, mitotic activity and the presence/absence of necrosis as major criteria distinguishing high grade and low grade tumors. Using these criteria, approximately 85% of MPNST are classified as high-grade tumors.

Most MPNST are clinically aggressive, high-grade tumors; most examples arise within deep soft tissues, viscera, or body cavities. Overall rates of recurrence and metastasis for MPNST have been reported to range from 40-65% and 30-60%, respectively.² Poor prognostic features include deep anatomic location, size greater than 5 cm, high tumor-grade (i.e. brisk mitotic activity, marked cytologic atypia, angio-invasiveness, and necrosis *en masse*), and positive surgical margins.¹ MPNST arising at deeper sites are often large and difficult to excise completely. In contrast, low grade cutaneous MPNST, like that seen in our case, behave much more indolently. Unlike high grade MPNST cases, the presence of positive surgical margins in patients having low grade MPNST did not negatively affect clinical outcome. Nearly 100% disease-specific survival has been reported in incompletely excised, low-grade MPNST cases after four years of follow-up.¹ Given its low-grade features, its

superficial anatomic location, and its negative surgical margin status, the risk of recurrence and metastasis in our case of eMPNST is very low.

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CONFLICT OF INTEREST

The authors have no conflict of interest to disclose.

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