Epithelioid malignant peripheral nerve sheath tumor arising in schwannoma

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Abstract

Epithelioid malignant peripheral nerve sheath tumor (EMPNST, malignant epithelioid schwannoma) is a rare variant of malignant peripheral nerve sheath tumor that has morphologic and immunophenotypic overlap with a variety of epithelioid neoplasms. Because of its rarity it may be potentially underrecognized. We describe a case arising in the subcutis of the thigh in a 25 year-old female, and discuss the pathologic features and differential diagnosis.

Keywords

Epithelioid malignant peripheral nerve sheath tumor, extremity, sarcoma, schwannoma, *SMARCB1/INI1* gene, thigh

Introduction

Epithelioid malignant peripheral nerve sheath tumor (EMPNST, malignant epithelioid schwannoma) is a rare variant of malignant peripheral nerve sheath tumor,[1–4] constituting only about 5% of these neoplasms. EMPNST can occur in both the superficial or deep soft tissues in similar distributions to conventional-type MPNST,[5] and the most frequent presentation is in the lower extremity or trunk of adults.[1] EMPNST has a slight male predominance and occurs most often in patients 20–50 years of age, although there is a wide age range.[3] This neoplasm can arise from the transformation of a pre-existing benign nerve sheath neoplasm, although this is typically schwannoma rather than neurofibroma.[2,3] While EMPNST can arise in association with neurofibromatosis type-1 (NF1), this is rare in comparison with conventional-type MPNST.

Although EMPNSTs tend to be aggressive lesions, with distant metastases eventually occurring in approximately 50% of patients, typically to the lungs, EMPNSTs occurring in superficial sites have been described to have a more favorable prognosis than those arising in a deep location.

Superficial EMPNST have been shown to have a metastatic rate of 12% compared to 30% for deep tumors,[4] but in contrast other studies have not shown a correlation between site/depth and clinical behavior.[1]

Histologically EMPNSTs are characteristically composed of nodules, clusters or cords of large polygonal or ovoid cells with prominent nucleoli, sometimes with focal rhabdoid morphology or clear cytoplasm. Often spindle cells typical of classical MPNST are also present, and merge with the epithelioid cells. Unlike conventional MPNST, EMPNSTs typically show diffuse and strong

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expression of S100 protein,[5] but they do not express melanoma-associated antigens such as MelanA and HMB45. There is rarely cytokeratin positivity,[4] while INI1 is lost in up to two thirds of EMPNST.[1,6] Inactivating somatic alterations of polycomb repressive complex 2 (PRC2) components *SUZ12* or *EED*, which leads to trimethylation loss at lysine 27 of histone H3 (H3K27me3), are present in up to 90% of MPNST (including those which occur sporadically, as well as those associated with radiotherapy or NF1). Loss of H3K27me3 by immunohistochemistry is noted in about half of MPNST, but this is usually retained in EMPNST.[7–11]

We describe an example of subcutaneous EMPNST of the thigh of a 25 year-old female, which showed diffuse S100 protein and SOX10 expression as well as loss of nuclear INI1. Because of the extreme rarity of this neoplasm, we illustrate how this can be mistaken for a variety of other epithelioid tumors at this site, with reference to the differential diagnosis.

Case report

The tumor presented as a mass in the right thigh of a 25 year-old female, who had noticed it for approximately 18 months prior to presentation. The patient had sensations of tingling along the leg when the lesion was knocked, but was otherwise asymptomatic and had no relevant past medical or family history. On examination, this was a small mobile, circumscribed subcutaneous mass and was clinically suspected to be a schwannoma arising from one of the cutaneous nerves supplying sensation to the lateral aspect of the thigh. No other lesions were present, and clinical examination, which included thorough examination for stigmata of NF1, and assessment of nodal status, was otherwise normal. Magnetic resonance imaging showed a solid, well-circumscribed, smoothly contoured ovoid mass measuring 21 mm × 11 mm × 11 mm in maximum diameter, present anteriorly to the quadriceps compartment of the right thigh at the junction of the biceps femoris and vastus lateralis, and suggesting a neurogenic tumor.

The tumor was diagnosed initially on core biopsy, with subsequent excision. The morphological findings in both the biopsy and the resection specimen were similar (Figure 1). Macroscopically the tumor measured 20 mm in maximum dimension and was located within subcutaneous fat. The tumor had a homogeneous, yellowish, myxoid cut surface. Microscopically the tumor was thinly encapsulated and lobulated (Figure 1(a)) and of variable cellularity (Figure 1(b and c)), and was composed of patternless distributions of slender spindle cells with minimally to mildly atypical vesicular nuclei and long cytoplasmic processes within delicately collagenous to focally myxoid stroma (Figure 1(a–c)), intermingled with more cellular nodules of plump, polygonal cells with moderately pleomorphic vesicular nuclei with prominent eosinophilic nucleoli and irregular chromatin, with moderate to abundant amounts of eosinophilic cytoplasm

(Figures 1(b and c)). The mitotic index was up to 2 per 10 high power fields (hpf) including markedly abnormal forms (Figure 1(c)). No lymphovascular invasion or necrosis was seen.

Immunohistochemically, the tumor was diffusely and strongly positive for S100 protein (Figure 1(d)), SOX10 (Figure 1(e)), D2-40, CD56 and glial fibrillary acidic protein in both the epithelioid and spindle cell populations, with focal CD34 expression. Epithelial membrane antigen (EMA) highlighted perineurial cells in the surrounding capsule, with some cytoplasmic expression in the epithelioid cells. There was complete loss of nuclear INI1 expression in the epithelioid cells (Figure 1(f)), although the spindle cells around the nodules of epithelioid cells retained INI1. The tumor was negative for HMB45, MelanA, smooth muscle actin, desmin, AE1/AE3, CD79a, CD45, and CD30. The features were of epithelioid malignant peripheral nerve sheath tumor. The tumor was excised with a thin fibrous capsule. In view of the size of the tumor, superficial location and low mitotic index, no adjuvant therapy was administered. The patient remains well, with no evidence of local recurrence or metastatic disease 20 months after excision of the neoplasm, but remains under six-monthly clinical follow-up.

Discussion

Although currently there are no specific histologic criteria to determine malignancy in epithelioid peripheral nerve sheath tumors, the present case had unequivocal malignant features, with marked cytological pleomorphism and atypical mitoses. One point of interest here is that although the epithelioid cells within this neoplasm were negative for INI1 immunohistochemically, the background slender spindle cells retained expression in nuclei. Both subsets of cell within the neoplasm were strongly S100 protein and SOX10 positive, confirming their Schwannian nature. This suggests that there are two different clones of cells within the tumor, one that appears cytologically benign and similar to the cells of a schwannoma, and another that appears cytologically malignant, that is, that this EMPNST is potentially arising within a schwannoma. It also suggests that loss of particular genetic material containing the *SMARCB1* (*INI1*) gene at 22q11.2, a negative cell cycle regulator and tumor suppressor gene,[12,13] may be involved in tumorigenesis.

The main differential diagnoses for EMPNST are carcinoma, myoepithelial carcinoma, melanoma, myxofibrosarcoma, epithelioid sarcoma and epithelioid schwannoma. Carcinoma, epithelioid sarcoma and melanoma can be distinguished readily using a simple immunohistochemistry panel for cytokeratins, S100 protein, MelanA and HMB45. Carcinomas and epithelioid sarcomas will be cytokeratin positive and S100 protein negative, in contrast to EMPNST. Melanomas are likely to express MelanA
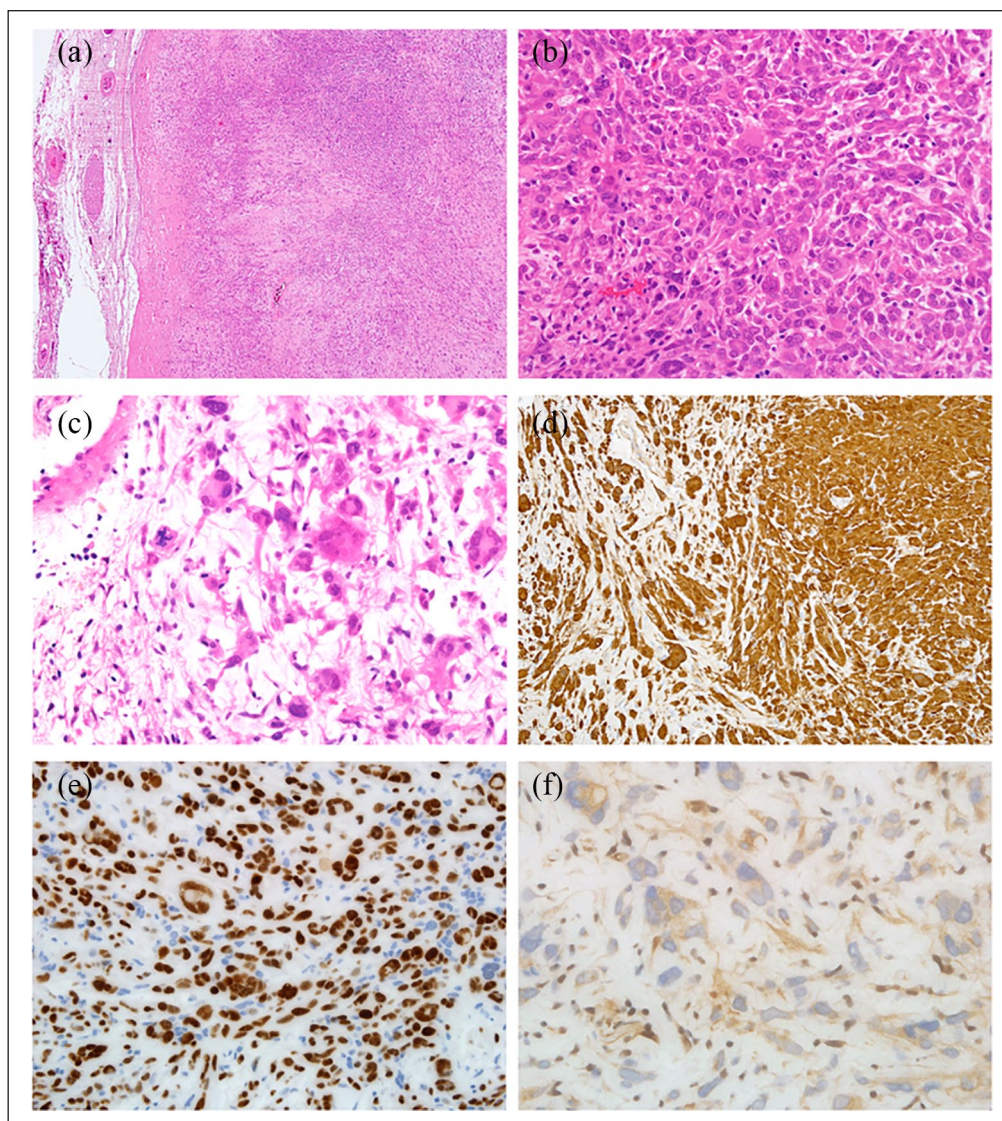
Figure 1. Epithelioid malignant peripheral nerve sheath tumor (EMPNST). The tumor is seen to be encapsulated and lobulated (a), and is of variable cellularity (a–c). It is composed of patternless distributions of slender spindle cells with minimally to mildly atypical vesicular nuclei and long cytoplasmic processes (a) within delicately collagenous (a) to focally myxoid stroma (c). There are also highly cellular nodules of plump, polygonal cells with moderately pleomorphic vesicular nuclei with prominent eosinophilic nucleoli and irregular chromatin, with moderate to abundant amounts of eosinophilic cytoplasm (b and c). Atypical mitotic figures can be seen (c). Immunohistochemically, the tumor shows diffuse, strong positivity for S100 protein (d), which is typical of EMPNST. The tumor also shows diffuse and strong nuclear expression of SOX10 (e). There is complete loss of nuclear INI1 expression in the epithelioid cells (f), in contrast to the interspersed small lymphocytes, which show nuclear retention of INI1.

and/or HMB45 in addition to S100 protein. It is rare for melanomas to only be MelanA and HMB45 positive without the expression of S100 protein, and it would be even more unusual to encounter such an entity as a metastasis without also having a history of melanoma with that immunophenotype. Myxofibrosarcoma with an epithelioid morphology is more likely to occur in the elderly, will be S100 protein-negative and should have areas with a more typical morphology: curvilinear vessels and sometimes vacuolated fibroblasts. Myoepithelial carcinoma may be more difficult to distinguish from EMPNST

because it is also typically S100 protein-positive (at least focally), and may also be INI1 negative. However, myoepithelial carcinoma should also display some cytokeratin and EMA positivity, in addition to expression of smooth muscle markers.[14,15] Epithelioid sarcoma typically shows strong cytokeratin expression with about 50% also showing strong CD34 positivity.[16]

Once these differential diagnoses are excluded, a distinction between epithelioid schwannoma and EMPNST must be made.[17] This is generally made by assessing the degree and extent of the cytological atypia, the nature of the mitoses

in the tumor and the presence or absence of necrosis. However, it has been reported that epithelioid schwannomas can have worrying nuclear atypia, as well as a relatively high mitotic count (up to nine mitoses per 10 hpfs), and these have been referred to as "atypical variants."[18] Therefore only atypical mitoses and necrosis can be safely used as absolute criteria for malignancy. More caution would need to be exercised when using the more subjective criteria of "extreme anaplasia," or when using a mitotic count of more than 10 mitoses per 10 hpf, as the upper limit of benign but mitotically active epithelioid schwannomas is still based on a limited number of cases.

The mainstay of management of localized EMPNST remains complete surgical resection with or without neoadjuvant/adjuvant radiation. The role of chemotherapy in the management of localized disease remains to be defined. A number of systemic therapies can be considered for advanced/metastatic EMPNST, but the evidence base is limited. The fact that a proportion of these tumors have INI1 loss suggests that patients should be recruited into trials of EZH2 inhibitors.

In summary, EMPNST is a rare soft tissue tumor and may be under reported. These tumors have immunohistochemical overlap with a number of other malignancies, which also makes the diagnosis challenging. Greater collaboration is required to define the underlying biology of EMPNST and explore potential novel therapies.

Declaration of conflicting interests

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