Superficial Malignant Peripheral Nerve Sheath Tumor

A Rare and Challenging Diagnosis

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Abstract

We reviewed the clinicopathologic features of 5 cases of malignant peripheral nerve sheath tumor (MPNST) manifesting in superficial locations associated with cutaneous neurofibromas (4 cases) or superficial peripheral nerve (1 case). Four cases had spindle cell morphologic features and were at least focally positive for S-100 protein, whereas the associated benign neural elements had more extensive S-100 immunoreactivity. The single epithelioid case was diffusely and strongly positive for S-100 protein. Melanoma markers, epithelial membrane antigen, glial fibrillary acidic protein, neurofilament, pancytokeratin (AE1/AE3), CD34, smooth muscle actin, and desmin were negative in all cases. There were no local recurrences, but 3 patients died of metastatic disease within 2 to 30 months (median, 21 months). MPNSTs can occur in a superficial location and may have an aggressive clinical course. Immunohistochemical markers are helpful in excluding other lesions in the differential diagnosis. However, identification of a benign precursor or origin from a nerve may be the most definitive way to properly classify these rare lesions.

Malignant peripheral nerve sheath tumors (MPNSTs) generally are regarded as sarcomas that occur in the deep soft tissues. Rarely, superficial primary MPNSTs with a cutaneous or subcutaneous origin have been reported.[1-11] Because MPNSTs are thought to arise from neurofibromas or peripheral nerves, both of which are found in superficial soft tissues, it follows that malignant transformation also can occur in these locations. Superficial MPNSTs often have a history of slow growth over a long period followed by a period of rapid growth. It is not uncommon to have a previous biopsy with a benign diagnosis and, subsequently, a recurrence with malignant transformation. However, because of their superficial location, they might come to clinical attention earlier and, historically, have been associated with a better overall outcome.[6-8] We describe the clinicopathologic features of 5 cases of superficial MPNSTs arising in cutaneous or subcutaneous tissue and review the existing English language literature regarding superficial MPNSTs.

Materials and Methods

We identified 5 cases of superficially located primary MPNSTs with a cutaneous or subcutaneous origin from the surgical pathology files at the University of Washington Medical Center, Seattle, and the Cleveland Clinic Foundation, Cleveland, OH. Superficial MPNST was defined as a lesion with its predominant and primary mass located in the dermis or subcutaneous tissue and not in contact with the fascia. All available diagnostic reports and medical records were reviewed. Clinical and gross information from consultation cases was provided with the cooperation

of consulting pathologists (cases included those reviewed on a consultation basis). H&E-stained sections were reviewed, and additional immunohistochemical stains were performed.

Immunohistochemical studies were performed with the avidin-biotin-peroxidase complex technique using the following commercially available antibodies: S-100 protein (polyclonal; dilution 1:8,000; DakoCytomation, Carpinteria, CA), neurofilament (2F11; dilution 1:4,000; DakoCytomation), pancytokeratin (AE1/AE3; 1:800 each; Boehringer Mannheim, Mannheim, Germany), epithelial membrane antigen (E29; dilution 1:1,000; DakoCytomation), desmin (D33; dilution 1:500; DakoCytomation), HMB-45 (HMB-45/50; dilution 1:50/1:250; courtesy of Allen Gown, MD, PhenoPath, Seattle, WA), MelanA (A103; dilution 1:200; DakoCytomation), tyrosinase (T311; dilution 1:25; Novocastra, Newcastle upon Tyne, England), glial fibrillary acidic protein (pGFAP; dilution 1:1,000; DakoCytomation), and microphthalmia transcription factor (D5; dilution 1:25; courtesy of David Fisher, MD, Dana Farber Cancer Institute, Boston, MA). Antibodies to myogenin (dilution 1:50; University of Washington Medical Center laboratory) and CD31 (JC70A; dilution 1:250; DakoCytomation) were used only in case 3.

Results

Clinical Findings

The clinical findings from the 5 cases of superficial MPNST are summarized in **Table 1**. Of the 5 cases, 4 occurred in women and 1 in a man. Patient age distribution was bimodal, with 3 younger patients (25, 18, and 27 years; cases 1, 3, and 4, respectively), and 2 older patients (79 and 74 years; cases 2 and 5, respectively). The patient in case 4 had a diagnosis of type 1 neurofibromatosis (NF-1) with a history of multiple plexiform neurofibromas. Cases 2 and 5 had a history of neurofibromas (cases not available for review) but did not have additional features of NF-1.

Case 1 occurred in a 25-year-old woman with a slowly growing midline neck mass that originally was thought to be a benign cyst. Case 2 was characterized by the slow growth of a hip mass during 15 years with recent increase in size. An 18-year-old woman (case 3) had no known history of neurofibromas but had a 2-year history of a mass near the knee. Of the 5 cases, 2 arose in the hip (cases 2 and 4), 1 in the distal thigh/knee (case 3), 1 in the wrist (case 5), and 1 in the midline of the neck (case 1). All cases were visible superficial masses without alterations noted in the skin surface.

All cases were treated with initial surgical excision with negative margins. Cases 2 and 4 also received adjuvant local radiation, and case 3 received adjuvant chemotherapy. Case 1 had limited follow-up owing to the recent diagnosis. In case 2, lung metastases developed 9 months after initial treatment, and the patient died of progressive metastatic pulmonary disease within 1 year of diagnosis. In case 3, a groin node metastasis was found only 4 months after diagnosis, and, despite chemotherapy, lung and bone metastases developed and the patient died of disease after 2.5 years. Case 4 had bone metastasis, and the patient died 2 months after surgery. Case 5 had no evidence of recurrence or metastasis within a 3-year follow-up, but renal cell carcinoma developed. None of the cases developed local recurrences. The median follow-up was 21 months.

Pathologic Findings

The pathologic findings are summarized in **Table 2**. The initial excisions included skin and subcutaneous fibroadipose tissue that contained tumor ranging in size from 2.5 cm (case 1) to 2 interconnected masses measuring 16 cm total (case 4). In cut sections, the lesions were described as solid, white to tan masses with a whorled appearance. The tumor masses were based predominantly in the deep dermis, with infiltration of the subcutaneous adipose tissue in cases 3 and 4 **Image 1**. Histologically, 4 of 5 cases arose from preexisting neurofibromas (cases 1, 2, 4, and 5), and case 3 was contiguous with a superficial peripheral nerve **Image 2**. Case 4, which occurred in a patient with NF-1, arose within a

Table 1
Clinical Features of Five Cases of Superficial Malignant Peripheral Nerve Sheath Tumor

Case No./Sex/ Age (y)	Tumor Location	History of NF	Treatment	Follow-up
1/F/25	Neck	No	Excision	Recent case
2/F/79	Right hip	No	Excision and radiation	DOD (1 y); lung metastases
3/F/18	Left distal thigh	No	Excision and chemotherapy	DOD (2.5 y); lung, lymph node, and bone metastases
4/F/27	Right hip	Diagnosis of type 1 NF	Excision and radiation	DOD (2 mo); metastatic to bone at diagnosis
5/M/74	Left wrist	No	Excision	NED (3 y)

DOD, died of disease; NED, no evidence of disease; NF, neurofibromatosis.

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Table 2
Pathologic Features of Five Cases of Superficial Malignant Peripheral Nerve Sheath Tumor

Case No.	Size (cm)	Histologic Features	Associated With Cutaneous NF	Mitoses per 10 HPF	Necrosis (%)	Depth of Invasion
1	2.5	Spindled with HR	Yes	35	0	Deep dermis; abuts subcutaneous adipose tissue
2	5.3	Spindled	Yes	>50	<5	Deep dermis; abuts subcutaneous adipose tissue
3	3	Spindled	No; tracks along peripheral nerve	7	0	Deep dermis and infiltrated subcutaneous adipose tissue
4	16	Spindled with HR	Yes (plexiform)	2	10	Deep dermis and infiltrated subcutaneous adipose tissue
5	2.6	Epithelioid	Yes	10	0	Deep dermis; abuts subcutaneous adipose tissue

HPF, high-power fields; HR, heterologous differentiation; NF, neurofibroma.

plexiform neurofibroma. Pacinian differentiation was prominent in cases 2 and 4 (Image 2C).

The malignant component in 4 cases had spindle cell morphologic features (cases 1-4), and 1 was epithelioid (case 5). The lesions with spindle cell cytomorphologic features were densely cellular and consisted of tight intersecting fascicles of spindle cells with scant cytoplasm and fine chromatin **Image 3A**. Mitoses ranged from 2 per 10 high-power fields (HPF; case 4) to focally greater than 50 per 10 HPF (case 2) with a median of 10 per 10 HPF. Focal necrosis was present in cases 2 and 4. Heterologous differentiation was seen in 2 cases. Areas of chondrosarcomatous and osteosarcomatous differentiation were seen in case 1, and case 4 had areas of rhabdomyosarcomatous and angiosarcomatous differentiation **Image 3B**.

The epithelioid MPNST (case 5) was characterized by dermal nests of large epithelioid cells with indistinct cytoplasmic borders and large, pleomorphic nuclei with prominent nucleoli **Image 3C**. The malignant cells infiltrated an often hyalinized stromal network containing frequent small hyalinized vessels. The tumor was based in the deep dermis and abutted the subcutaneous adipose tissue without infiltrating it. There was no involvement of the overlying epidermis.

Immunohistochemical Analysis

Immunohistochemical stains for S-100 protein were focally positive in the sarcomatous areas of all cases. As might be expected, the spindle cell MPNSTs showed weaker and much less extensive S-100 protein immunoreactivity than the adjacent neurofibromas and peripheral nerves **Image 4A**. In contrast, the epithelioid variant of MPNST (case 5) stained uniformly and strongly for S-100 protein, to an even greater degree than the neurofibroma associated with it **Image 4B**. Neurofilament antibodies similarly stained only benign neural elements. All cases were negative for melanoma markers HMB-45, MelanA, tyrosinase, and microphthalmia transcription factor. CD34 revealed numerous small vessels in cases 1 and 2 but did not react with the neoplastic cells, with the exception of the angiosarcomatous component of case 4.

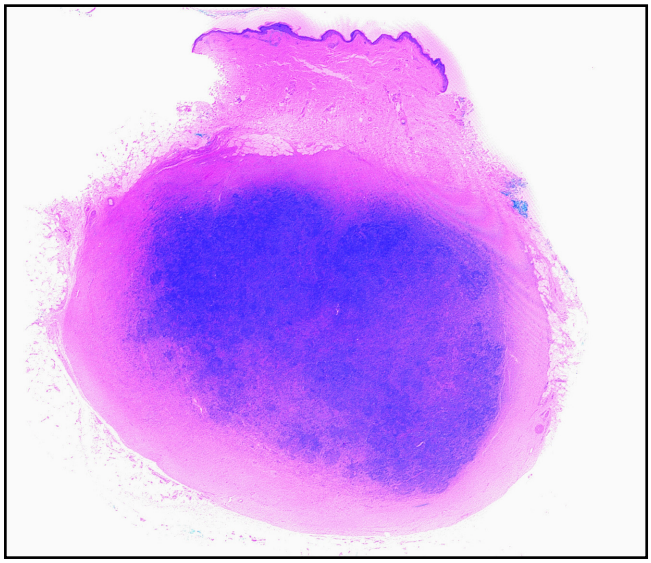

Image 1 (Case 5) Scanned image showing a mass located within the deep dermis (H&E, ×1).

The rhabdomyoblasts in case 4 were immunoreactive for desmin and myogenin, and the angiosarcomatous component of this case was positive for CD34 and CD31. The chondrosarcomatous component of case 1 was strongly positive for S-100 protein, in contrast with the malignant spindle cells.

Discussion

Superficial MPNSTs are extremely rare, with a limited number of cases reported in the literature. In the available case records at the University of Washington and the Cleveland Clinic from January 1990 to December 2003, only 5 cases met our criteria for the diagnosis of superficial MPNST. Like their deep soft tissue counterparts, superficial MPNSTs often are associated with neurofibromas. Some authors have suggested a direct connection of the tumor with a nerve or a neurofibroma as a criterion for the diagnosis of MPNST.[11] All 5 of our cases arose from an identifiable superficial peripheral nerve (1

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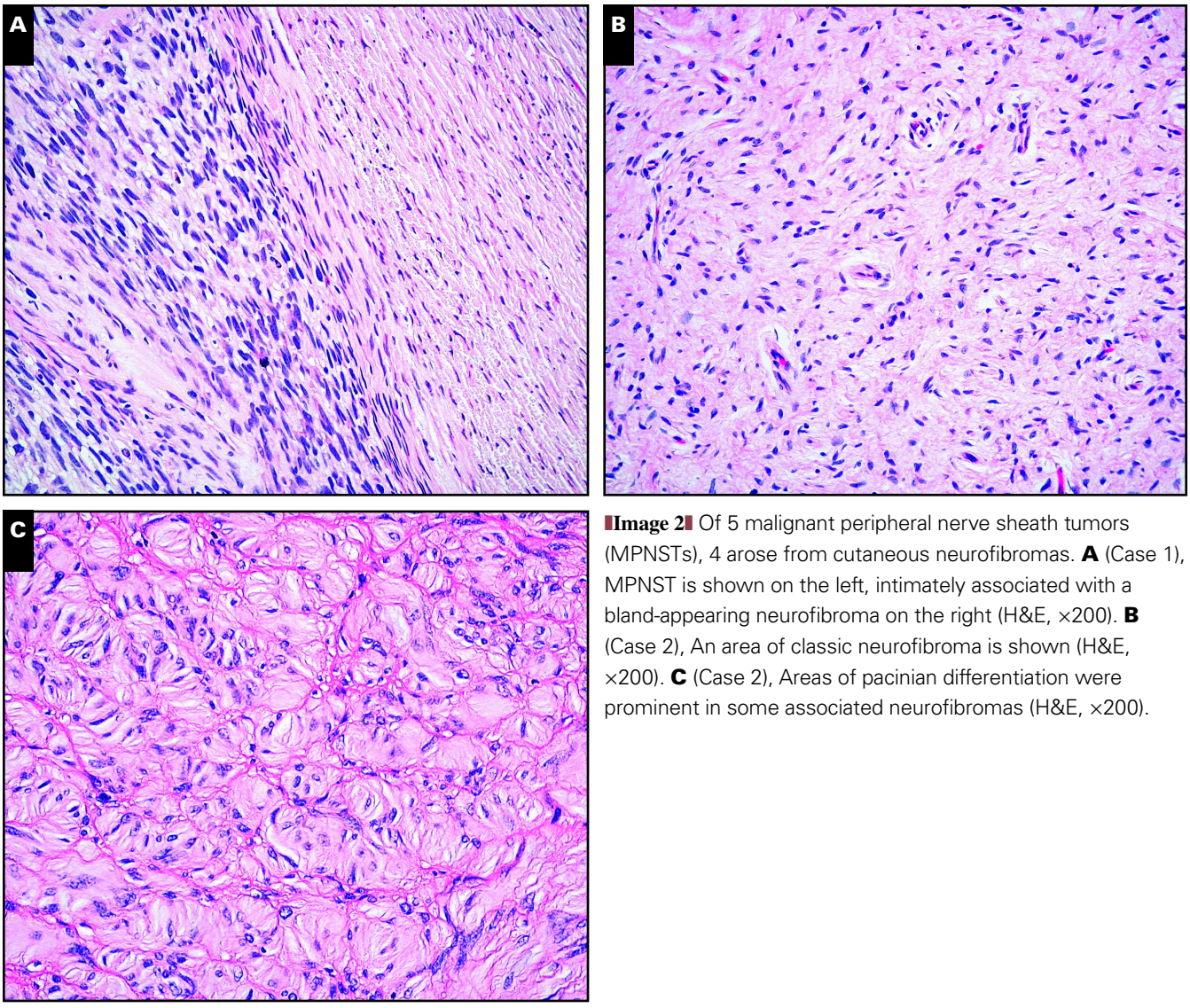

Image 2 Of 5 malignant peripheral nerve sheath tumors (MPNSTs), 4 arose from cutaneous neurofibromas. **A** (Case 1), MPNST is shown on the left, intimately associated with a bland-appearing neurofibroma on the right (H&E, ×200). **B** (Case 2), An area of classic neurofibroma is shown (H&E, ×200). **C** (Case 2), Areas of pacinian differentiation were prominent in some associated neurofibromas (H&E, ×200).

case) or a neurofibroma (4 cases). In our review of the English language literature, using strict diagnostic criteria (dermal or subcutaneously based tumors associated with a cutaneous neurofibroma or clinical diagnosis of NF-1), we found 23 additional cases of conventional superficial MPNST reported in adults **Table 3**.[6-11]

The 4 cases of conventional MPNST reported herein occurred in a wide age range (18-79 years; median, 27 years); 3 cases occurred in patients younger than 30 years. Case series of conventional deep soft tissue MPNSTs have reported similar age ranges of 7 to 75 years (median, 34 years).[13] The 27-year-old patient in our series (case 4) was the only patient who had a definite diagnosis of NF-1. Younger age at diagnosis has been associated with NF-1.[13] In our literature review of 23 cases of conventional superficial MPNSTs and our 4 cases (total, 27 cases), 10 (37%) were associated with NF-1, in contrast with the 52% associated with deeply situated tumors.

One might postulate that superficial tumors would be identified at a smaller size than their deep-seated counterparts. We found that 12 (46%) of reported superficial MPNSTs with information on size available (n = 26) were larger than 5 cm at diagnosis, whereas 54 (61%) of deep MPNSTs (n = 88) in the series by Ducatman et al[13] were larger than 5 cm at diagnosis. In addition, in comparison with deep-seated MPNSTs, superficial cases were reported more often in the head and neck region (15/27 [56%]), but they also occur in the trunk and extremities, as seen in 4 of our cases.

The natural history of superficial MPNST is not as well established as that for the deeper lesions, which usually have a poor prognosis. In a series of 120 MPNSTs by Ducatman et al,[13] the overall 5- and 10-year survival rates were 34% and 23%, respectively (Table 3). In contrast, our review of the literature found that 16 (62%) of 27 patients with conventional superficial MPNSTs had no evidence of disease and 2 (8%)

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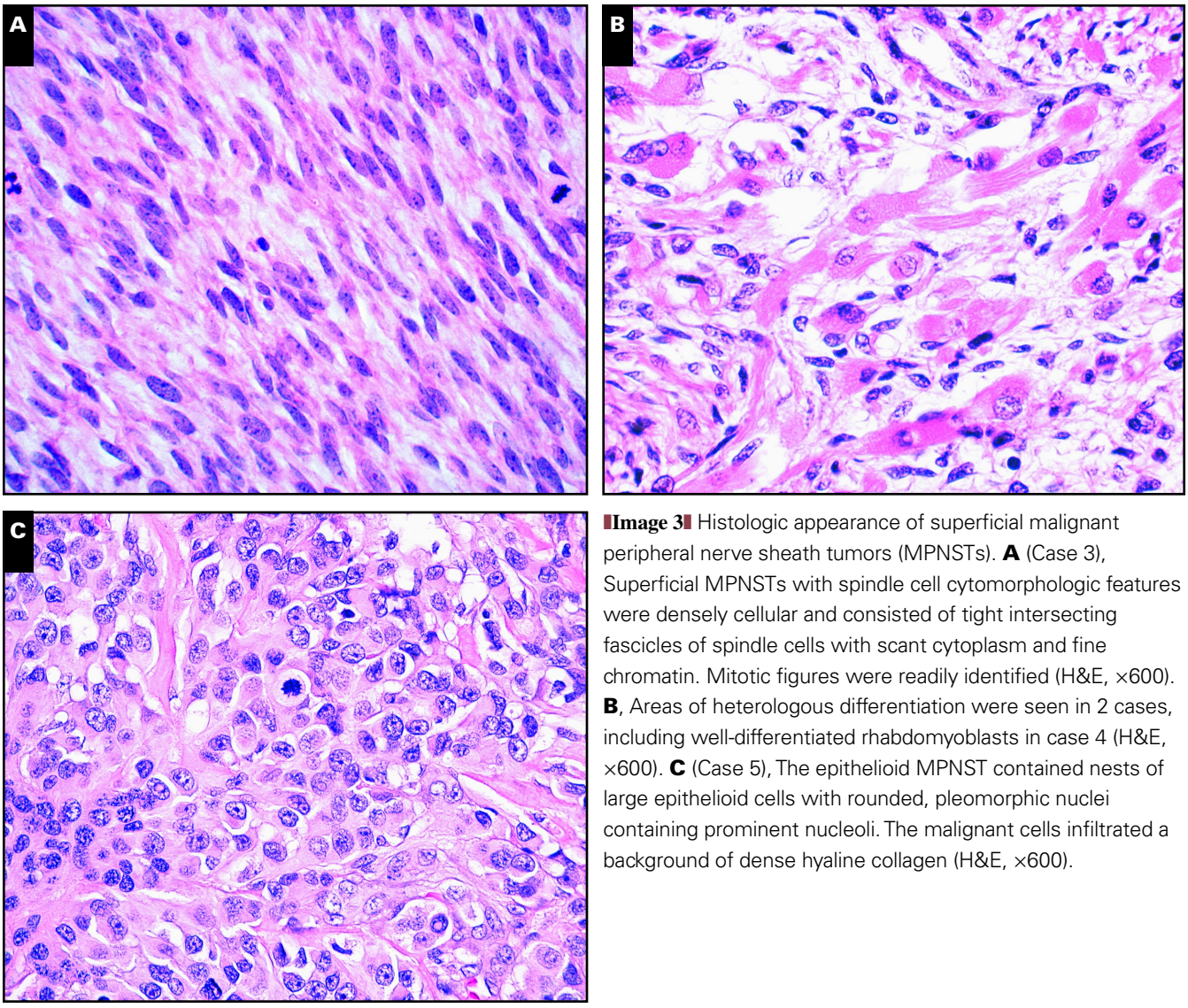

Image 3 Histologic appearance of superficial malignant peripheral nerve sheath tumors (MPNSTs). **A** (Case 3), Superficial MPNSTs with spindle cell cytomorphologic features were densely cellular and consisted of tight intersecting fascicles of spindle cells with scant cytoplasm and fine chromatin. Mitotic figures were readily identified (H&E, ×600). **B**, Areas of heterologous differentiation were seen in 2 cases, including well-differentiated rhabdomyoblasts in case 4 (H&E, ×600). **C** (Case 5), The epithelioid MPNST contained nests of large epithelioid cells with rounded, pleomorphic nuclei containing prominent nucleoli. The malignant cells infiltrated a background of dense hyaline collagen (H&E, ×600).

were alive with disease, with a mean follow-up of 3.3 years (Table 3). In the largest series of superficial MPNSTs, Dabski et al[6] reported that although 78% of their 13 cases recurred after local excision with a mean relapse-free period of approximately 5 years, the overall 4-year survival rate was 66%.

One might also postulate that superficial MPNSTs have a better prognosis than their deep-seated counterparts because they come to clinical attention earlier. However, Khoo and Foo[7] described a series of 7 cases of superficial neurofibromas with "malignant change" ranging in size from 5 to 20 cm (median, 10.5 cm) that were present for 2 to 13 years before a diagnosis of neurofibrosarcoma was made. Of the 7 cases, 4 actually had previous biopsies or excisions of the same lesion with a diagnosis of neurofibroma. The malignant diagnosis often was made after a period of rapid growth. The largest tumors (two 20-cm masses and one 15-cm mass) manifested at higher stages and were associated with poor outcomes (recurrence, metastasis, or death). However, the remaining 4 cases (size range, 5-10 cm) reportedly were recurrence-free with follow-up of 8 to 48 months. The success of these cases was attributed largely to excisions with wide tumor-free margins because this is technically more feasible when a tumor is smaller and does not involve a proximal nerve trunk, as occurs more frequently with deep-seated tumors. This also is the trend with other sarcomas. For example, superficial/cutaneous leiomyosarcoma has a much better prognosis than do deep-seated lesions.[12]

The generally favorable prognosis of superficially located sarcomas contrasts with our series, in which 3 of 4 cases with meaningful follow-up were associated with an aggressive clinical course, including pulmonary and bone metastases with death occurring within 2 months to 2.5 years. These poor outcomes occurred despite relatively small tumor size at diagnosis in 2 cases (case 2, 5.3 cm; case 3, 3 cm), reexcisions with

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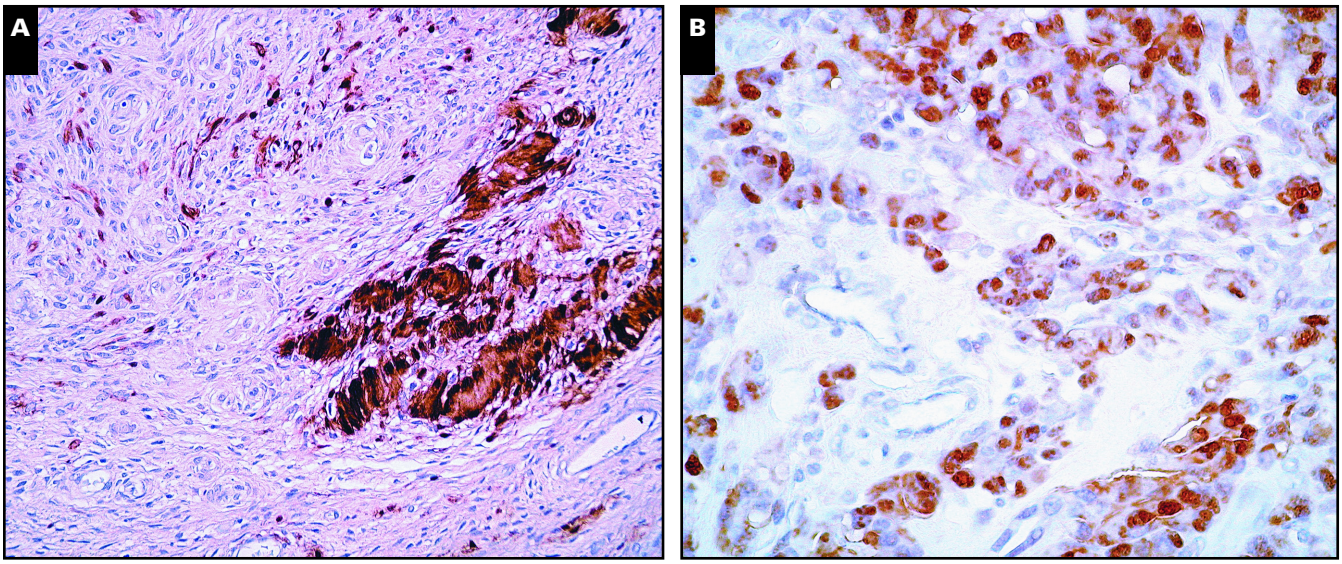

Image 4 S-100 protein antibody staining of malignant peripheral nerve sheath tumors (MPNSTs). **A** (Case 4), The adjacent neurofibromas stained more uniformly with S-100 protein antibodies than the malignant spindle cell components of the lesion (S-100, ×100). **B** (Case 5), In contrast, the epithelioid MPNST had uniform strong cytoplasmic immunoreactivity (S-100, ×400).

Table 3
Comparison of Features of Deep and Superficial Conventional MPNSTs*

	Deep Soft Tissue MPNSTs (n = 120)[13]	Superficial MPNSTs (n = 27)[6-11†]
Sex		
M	68 (57)	17 (63)
F	52 (43)	10 (37)
Mean (range) age at diagnosis (y)	34.0 (7-75)	40.0 (4-79)
Neurofibromatosis type 1–associated	62 (52)	10 (37)
Site		
Head and neck	23 (19)	15 (56)
Trunk	55 (46)	7 (26)
Upper extremity	8 (7)	2 (7)
Lower extremity	34 (28)	3 (11)
Size >5 cm	54/88 (61)	12/26 (46)
Recurrence	50 (42)	17 (63)
Mean time from diagnosis (mo)	21.6	38.0
Metastases	33 (28)	7 (26)
Mean time from diagnosis (mo)	34.5	30.0
Survival		Mean, 3.3y NED, 16 (62) AWD, 2 (8) DOD, 8 (31)
5-y	41 (34)	—
10-y	28 (23)	—

AWD, alive with disease; DOD, died of disease; MPNST, malignant peripheral nerve sheath tumor; NED, no evidence of disease.
* Data are given as number (percentage) or number/total (percentage) unless otherwise indicated.
† And present study.

negative margins, and adjuvant radiation or chemotherapy. It is interesting that when available outcomes for 27 reported cases of superficial MPNSTs were compiled, recurrence and metastasis rates were similar in superficial and deep MPNSTs (Table 3). However, survival rates seemed to be better for superficial lesions with 62% of cases (16/27) with no evidence of disease after a mean follow-up of 3.3 years. The more aggressive behavior of superficial MPNSTs in our series is notable, but the small sample and possible selection bias of consultation material also should be acknowledged. However, the rarity of such malignant neoplasms effectively precludes larger case-controlled studies.

The differential diagnosis of superficial MPNST includes benign entities such as neurofibroma, cellular schwannoma, benign fibrous histiocytoma, and leiomyoma. The presence of infiltrative borders, increased cellularity with nuclear atypia, and more frequent mitoses should help distinguish MPNST from benign superficial lesions. Other considerations with aggressive or malignant potential include spindle cell or desmoplastic melanoma, fibrosarcomatous dermatofibrosarcoma protuberans, metaplastic carcinoma, myxofibrosarcoma, and cutaneous metastases from deep-seated sarcomas. The presence of alternating cellular and more myxoid areas and wavy, tapered nuclei suggests MPNST in cases that do not have a clearly associated nerve or neurofibroma. The neoplastic cells also may be concentrically or radially arranged around vessels. However, some cases with uniform fascicles of spindle cells can be difficult to distinguish from fibrosarcomatous dermatofibrosarcoma protuberans or monophasic synovial sarcoma without the aid of immunohistochemical and molecular studies.

Kikuchi et al[14] described 2 "solitary cutaneous malignant schwannomas" of the head and neck that were not associated with a nerve trunk or neurofibroma. The diagnosis was based on S-100 protein immunoreactivity (with negative HMB-45 staining) and an absence of melanosomes by electron

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microscopy. However, these criteria are not specific for the diagnosis of MPNST, and, in our opinion, these lesions could represent amelanotic spindle cell melanomas. We caution against making the diagnosis of MPNST on the basis of immunohistochemical analysis alone because spindle cell melanomas, which are a much more common cutaneous malignant neoplasm, usually are diffusely and strongly positive for S-100 protein, frequently are negative for other melanoma markers, and might not have an associated junctional component. MPNSTs usually have much less extensive immunoreactivity for S-100 protein (with the exception of the epithelioid type), and approximately 50% of MPNSTs are completely negative for this antigen.[6] In conjunction with clinical evidence of NF-1 or origin from a nerve or neurofibroma, focal to moderate S-100 protein positivity can support the diagnosis of MPNST in superficial locations. All of our cases stained at least focally with S-100 protein, but the immunoreactivity was much more focal than usually is seen in melanoma, with the exception of the epithelioid case, which was diffusely positive (case 5).

The epithelioid variant of MPNST, formerly called malignant epithelioid schwannoma, is estimated to account for between 5% and 17% of MPNSTs.[8,15-18] They occur more frequently in superficial locations, where they seem to have a slightly better prognosis and are not associated with NF-1.[8,15,16] The largest series consisted of 26 cases of epithelioid MPNST, including 16 superficial and 10 deep-seated tumors.[8] Six of these lesions were associated with a benign nerve sheath tumor and 15 with a peripheral nerve. The superficial cases generally were smaller than those in deep tissue (median size, 3.5 vs 5 cm, respectively). The majority of deep and superficial cases occurred in the extremities; no cases occurred in the head and neck region. Superficial lesions were treated adequately with wide local excision alone with the exception of 1 case in which lung metastasis developed. In contrast, 3 of the 10 deep-seated tumors had lethal metastatic disease within 3 years of diagnosis. Case 5 in our series was an epithelioid MPNST. It occurred in the deep dermis of the wrist and was associated with a cutaneous neurofibroma. It did not recur after complete excision within a 3-year follow-up period.

Epithelioid MPNST might be very difficult to differentiate from amelanotic melanoma, but the presence of immunoreactivity for other melanoma markers such as tyrosinase, MelanA, and HMB-45 and the presence of a junctional component are useful in differentiating melanoma from epithelioid MPNST. In contrast with MPNST with spindle cell morphologic features, the epithelioid variant often displays more uniform S-100 protein staining. Case 5 in our series was diffusely and strongly positive for S-100 protein, with even more uniform S-100 protein immunoreactivity than the neurofibroma with which it was associated.

The presence of heterologous elements in some MPNSTs is theorized to occur because of divergent ectomesenchymal differentiation.[19] Case 4 in our series had both rhabdomyosarcomatous and angiosarcomatous differentiation. This case also was quite aggressive, with metastatic disease present at diagnosis resulting in death within 2 months. It is interesting to note that the bone metastases in this case were composed largely of the angiosarcomatous component seen within the primary tumor. Case 1 in our series also had heterologous chondrosarcomatous and osteosarcomatous elements. Because of the recent diagnosis of this case, the long-term behavior of this tumor cannot be evaluated. The patient did not have metastatic disease at initial diagnosis.

The diagnosis of MPNST should be considered in the differential diagnosis of a superficial spindle cell or epithelioid neoplasm. Superficial MPNSTs occur sporadically and in association with NF-1 and are reported more frequently in the head and neck region than deep MPNSTs. They tend to be smaller at initial diagnosis than deep-seated tumors and might have a better overall prognosis. However, they might have similar recurrence and metastasis rates. Superficial MPNSTs certainly can have an aggressive course with poor outcomes, as was the case with 3 of 5 cases in the present series. Careful exclusion of more common cutaneous tumors, such as spindle cell melanoma, might prove difficult in cases without an associated nerve or neurofibroma.

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