Malignant neuroectodermal tumor with melanocytic and rhabdomyoblastic differentiation

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Abstract

Malignant melanoma can metastasize widely and vary significantly in its histological appearance; it rarely presents as a deep-seated mass without an obvious primary site elsewhere. Malignant peripheral nerve sheath tumor (MPNST) is a high-grade sarcoma characterized by conventional and epithelioid subtypes. MPNST can demonstrate heterologous differentiation, usually in the form of osteosarcomatous, chondrosarcomatous, or rhabdomyosarcomatous differentiation. MPNST does not harbor true melanocytic differentiation, although epithelioid MPNST typically is diffusely S-100 protein positive and superficially can resemble malignant melanoma. An unusual intra-abdominal mass was recently encountered with features of both melanoma and conventional or epithelioid MPNST containing a fascicular spindle cell component, an epithelioid component with melanocytic differentiation, as well as a rhabdomyosarcomatous component. The terminology "malignant neuroectodermal tumor with melanocytic and rhabdomyoblastic differentiation" is proposed to describe this neoplasm, reflecting the unusual concomittant lines of differentiation as well as offering a possible rationale for nosologically challenging aspects of this neoplasm.

Introduction

The neural crest, derived from embryonic neuroectoderm, is thought to give rise to several cell types within the human body including melanocytes and Schwann cells.[1] The prototypic malignant neoplasms arising from or showing differentiation toward these cell types are malignant melanoma and malignant peripheral nerve sheath tumor (MPNST), respectively. Malignant melanoma is a relatively common neoplasm arising predominantly in the skin, but also the eye, oral and anogenital mucosal surfaces, esophagus, and meninges. A small number of metastatic melanomas present with no clearly identifiable primary site. Because of its ability to metastasize to a wide variety of sites as well as its wide histological spectrum, its ability to mimic other neoplasms is well recognized. Although spindle cell melanomas often lose immunoreactivity for melanocyte-specific markers (HMB-45, Melan-A, tyrosinase, MiTF), they are virtually all positive for S-100 protein.[2] MPNST comprises five to ten percent of all soft tissue sarcomas with a peak incidence in the third to sixth decades of life. Approximately twenty-five to fifty percent of MPNST are associated with neurofibromatosis-1.[3,4] MPNST often arises in a pre-existing neurofibroma but can involve practically any anatomic site in the body. In general, they are considered to be high-grade sarcomas with a high likelihood of local recurrence and distant metastasis.

The typical conventional MPNST is a fascicular, spindle cell sarcoma with variable immunoreactivity for S-100 protein; it is not uncommon for conventional MPNST to be only focally positive for S-100 or lack staining for the antigen altogether. Of particular interest is the tendency for MPNST to contain areas with heterologous differentiation, most commonly osteosarcomatous, chondrosarcomatous, or rhabdomyosarcomatous differentiation (malignant Triton tumor).[4] Epithelioid MPNST accounts for five percent of all MPNST. In contrast to the conventional subtype, these neoplasms have a nested growth pattern, an epithelioid cytomorphology with prominent nucleoli, as well as strong and diffuse positivity for S-100 protein; thus bearing a superficial resemblance to melanoma. Many epithelioid MPNST also have a minor spindle cell component which resembles conventional MPNST. Significantly, epithelioid MPNST is negative for melanocyte-specific markers (e.g. HMB-45, Melan-A, etc.).[4]

An exceptional intra-abdominal neoplasm was recently encountered in consultation with features of both MPNST and melanoma including a fascicular spindle cell component consistent with conventional MPNST, extensive rhabdomyosarcomatous differentiation, as well as an epithelioid component reminiscent of epithelioid MPNST but showing melanocytic differentiation. Review of the English language literature revealed one other similar case, a case of an MPNST with divergent melanocytic and rhabdomyoblastic differentiation.[5]

Materials and Methods

This case was received in consultation by one of the authors (BPR). Immunohistochemistry was performed on formalin-fixed, paraffin-embedded tissue by the avidin-biotin-peroxidase complex technique using commercially available antibodies to the following antigens: S-100 (polyclonal; 1:8000; DAKO, Carpinteria, CA, USA), HMB-45/50 (HMB 45/50 cocktail, 1:50/1:250 A. Gown), tyrosinase (T311, 1:100, Novocastra, Norwell, MA), Melan-A (A103, 1:200, DAKO, Carpinteria, CA, USA), and microphthalmia transcription factor (D5, 1:25, R. Schmidt).

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Key words: malignant peripheral nerve sheath tumor, malignant melanoma, melanocytic differentiation, rhabdomyoblastic differentiation, malignant neuroectodermal tumor.

Contributions: MRT and BPR, contributed to the concept and design of the study, as well as the analysis and interpretation of the data. They both helped draft/revise the article and gave final approval of the version to be published.

Conflict of interest: the authors report no conflicts of interest.

Received for publication: 26 July 2009.
Accepted for publication: 5 August 2009.

Rare Tumors 2009; 1:e26
doi:10.4081/rt.2009.e26

Results

Clinical features

The patient was a 67-year old man who presented with a large mass in the abdomen requiring resection of the spleen, a portion of the pancreas, as well as a segment of colon and small bowel. Approximately one year subsequent to diagnosis of the abdominal mass, the patient presented with a brain metastasis.

Pathological features

Grossly, the intra-abdominal mass was 20 cm in greatest dimension. Histologically, it was characterized by a proliferation of spindle cells with enlarged hyperchromatic nuclei with tapered ends and faintly eosinophilic cytoplasm arranged in intersecting fascicles. A prominent herring-bone pattern could be

observed in several fields (Figure 1A). Other areas consisted of epithelioid cells with a moderate amount of eosinophilic cytoplasm and enlarged vesicular nuclei with prominent nucleoli (Figure 1B). A third pattern was characterized by rhabdomyoblasts containing abundant eosinophilic cytoplasm with eccentrically placed, enlarged nuclei and prominent nucleoli, representing rhabdomyosarcomatous heterologous differentiation (Figure 1E). Mitotic activity was brisk throughout the neoplasm and tumor necrosis was present.

S-100 protein was only focally positive in the fascicles of spindle cells, but strongly and diffusely positive in the epithelioid areas (Figure1C). Melanocytic markers including HMB-45/50 (Figure 1D), Melan-A, tyrosinase, and MITF were strongly and diffusely positive in the epithelioid component but were absent from the spindle cell component. Fontana-Masson staining did not demonstrate any melanin pigment in either the epithelioid or spindle cell components. Skeletal muscle differentiation was confirmed in the rhabdomyoblasts by strong and diffuse immunoreactivity for desmin (Figure 1F) and myogenin.

The brain metastasis was characterized by a morphological appearance similar to the epithelioid component of the abdominal mass, including epithelioid cells with eosinophilic cytoplasm, enlarged vesicular nuclei, and prominent nucleoli (Figure 2A). The brain metastasis was focally positive for S-100 protein, and variably positive for Melan-A (Figure 2B) and HMB-45.

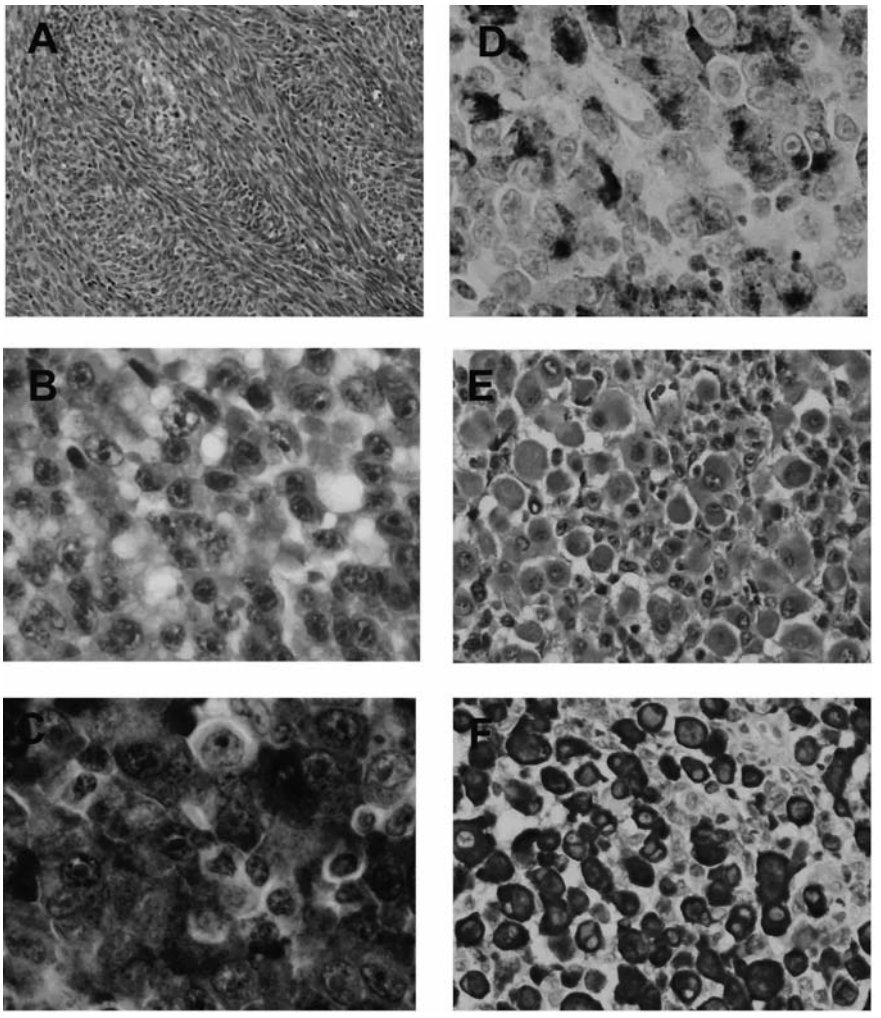

Figure 1. Abdominal mass. (A) Fascicular spindle cell component; (B) epithelioid component with prominent nucleoli; (C) strong and diffuse immunoreactivity for S-100 protein in the epithelioid component; (D) uniform staining for HMB-45 in the epithelioid component; (E) rhabdomyoblasts in areas of rhabdomyosarcomatous heterologous differentiation; (F) strong and diffuse immunoreactivity for desmin in rhabdomyoblasts.

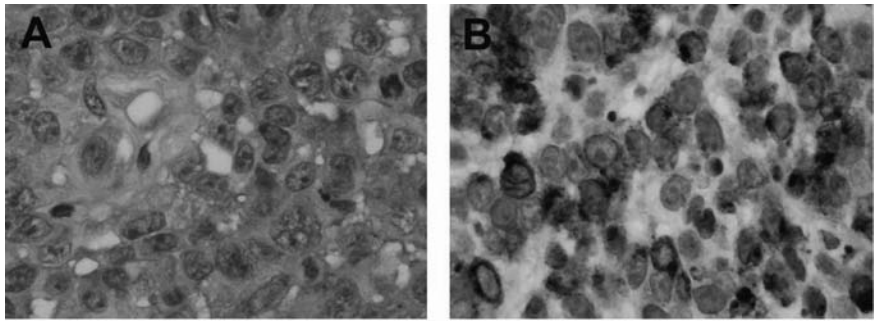

Figure 2. Metastasis to brain. (A) Epithelioid neoplasm similar in appearance to the primary neoplasm shown in Figure 1B, (B) immunohistochemistry showing positivity for Melan-A.

Discussion

The chief differential diagnoses in this case are malignant melanoma and MPNST. One possibility is that the neoplasm is a melanoma with a significant spindle cell component and heterologous rhabdomyosarcomatous differentiation. Melanocytic neoplasms displaying rhabdomyosarcomatous differentiation have been reported in the literature. Four case reports have described rhabdomyosarcomas arising within congenital melanocytic nevi, demonstrating that cells with committed melanocytic differentiation can undergo differentiation toward a skeletal muscle phenotype.[6-8] There is also a report of two patients with congenital melanocytic nevi who subsequently developed melanomas within their nevi showing areas of rhabdomyoblastic differentiation.[9] In addition, the metastasis involving the brain is both clinically and pathologically more suggestive of malignant melanoma than MPNST.

Another possibility is that this tumor represents an MPNST with a conventional spindle cell component, heterologous rhabdomyoblastic differentiation, and an epithelioid component (reminiscent of epithelioid MPNST) that happens to show evidence of melanocytic differentiation. This diagnosis is supported by the following features. First, deep-seated primary melanomas (this patient had no other known primary), though possible, are rare. On the other hand, MPNST commonly occurs in a deep-seated location. Furthermore, the spindle cell component was only focally positive for S-100 protein and was negative for melanocyte-

specific markers, which is much more typical of MPNST than spindle cell melanoma (which is often strongly positive for S-100 protein, as mentioned previously). In addition, the phenomenon of rhabdomyoblastic differentiation is a relatively common occurrence in MPNST, compared to its case-reportable status in melanoma. The feature of this case that is most difficult to reconcile with the diagnosis of MPNST is the epithelioid component, which showed evidence of melanocytic differentiation. Although epithelioid MPNST can be strongly positive for S-100 protein, melanocyte-specific markers such as HMB-45 and Melan-A should be negative. There are rare cases, however, of MPNST that have been noted to demonstrate melanocytic differentiation.[10-15]

With the difficulties definitively classifying the neoplasm as either a melanoma or MPNST, we propose that an alternative term be used: malignant neuroectodermal tumor with melanocytic and rhabdomyoblastic differentiation. As alluded to earlier, the term "neuroectodermal tumor" is used to refer to the fact that both Schwann cells and melanocytes are derived from the neural crest, which in turn is derived from embryonic neuroectoderm.[1] Neoplasms with features of melanocytic and schwannian differentiation are not difficult to find. Nevi with so-called "neurotization" of dermal nevomelanocytes are one example. Melanotic schwannoma is a well-described entity that occurs sporadically and in the setting of Carney's complex (cardiac and cutaneous myxomas, pigmented nevi, endocrine abnormalities, and melanotic schwannomas), and can on occasion metastasize (10-20%). The neoplastic cells in melanotic schwannoma can be epithelioid to spindled, and can contain prominent nucleoli. In addition to being strongly S-100 protein positive and HMB-45 positive, melanotic schwannomas contain true melanin pigment, which stains positively with Fontana-Masson stain. Ultrastructurally, they are noted to contain premelanosomes and melanosomes.[16] Melanin-containing neurofibromas have been described also. Fetsch *et al.* (2000) characterized a series of 19 pigmented "melanotic" neurofibromas including diffuse, plexiform, diffuse/plexiform combined, and intraneural epithelioid morphologies, which exhibited immunopositivity for S-100 protein, HMB-45, Melan-A, and tyrosinase, as well as melanin pigment, confirmed with Fontana-Masson stain.[17] Furthermore, melanin-containing nerve sheath tumors have been described in a neurofibromatosis rat model (induced by transplacental administration of ethylnitrosurea).[18]

Because both MPNST and melanoma are thought to arise from or show differentiation toward neural crest-derived cells, it is not surprising that rare cases of melanoma might show rhabdomyoblastic differentiation while rare cases of MPNST might demonstrate melanocytic differentiation. However, as discussed previously, a rigid rendering of the diagnosis of either melanoma or MPNST to the exclusion of the other in this case is not easily done, nor does it capture its diagnostic nuances. Instead of forcing this neoplasm into the diagnostic category of melanoma or MPNST, a more encompassing nomenclature such as malignant neuroectodermal tumor may be appropriate. In the end, cases such as this help us to re-evaluate our diagnostic criteria and highlight possible relationships between different entities.

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