Malignant Peripheral Nerve Sheath Tumor With Rhabdomyosarcomatous Differentiation (Malignant Triton Tumor)

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• Malignant peripheral nerve sheath tumors arise from Schwann cells or within existing neurofibromas and have a strong association with type 1 neurofibromatosis. These tumors are histologically diverse and may contain malignant areas of divergent mesenchymal differentiation, the most common of which is skeletal muscle (rhabdomyosarcoma). Malignant peripheral nerve sheath tumor with rhabdomyosarcomatous differentiation is also known as malignant triton tumor. Malignant triton tumor has a worse prognosis than classic malignant peripheral nerve sheath tumor does, and the correct diagnosis requires attention to the clinical history and knowledge of the complexities regarding its differential diagnosis. In this review we discuss the clinical, histopathological, immunohistochemical, and prognostic features of this rare neoplasm.

(*Arch Pathol Lab Med.* 2006;130:1878–1881)

Malignant tumors arising from Schwann cells of peripheral nerves or within existing neurofibromas are collectively referred to as malignant peripheral nerve sheath tumors (MPNSTs). On occasion, these tumors may contain other malignant mesenchymal components, the most common of which is skeletal muscle (rhabdomyosarcoma). Malignant peripheral nerve sheath tumor with rhabdomyosarcomatous differentiation is also known as malignant triton tumor (MTT).

Rhabdomyosarcomatous elements within MPNSTs were first described by Masson in patients with neurofibromatosis.[1] Masson theorized that Schwann cells were capable of inducing muscular differentiation of other endoneurial cells. A more widely accepted theory for the origin of these tumors, also put forth by Masson, is the metaplastic theory, according to which malignant Schwann cells transform directly into striated muscle cells. The Schwann cells, being of neural crest origin, may retain a capacity for mesenchymal differentiation during malignant transformation.[2] The name *triton* was first used by Woodruff et al[3] in reference to work done by Locatelli[4] in which supernumerary limbs containing bone and muscle were induced to grow on the backs of triton salamanders via the implantation of the sciatic nerve into the soft tissues of the back.

To determine whether or not a tumor is truly a MTT, Woodruff et al proposed 3 criteria: (1) the tumor arises along a peripheral nerve, in a ganglioneuroma, or in a patient with type 1 neurofibromatosis (NF1), or represents a metastasis from such a tumor; (2) the tumor has the growth characteristics of a Schwann cell tumor; and (3) rhabdomyoblasts can be demonstrated arising within the body of the tumor.[3]

The MPNSTs as a group account for approximately 5% to 10% of all soft tissue sarcomas.[5] These tumors arise either in association with peripheral nerves or within preexisting neurofibromas. An MPNST often arises in the clinical setting of NF1, although sporadic cases do occur. These tumors may also arise in sites of previous irradiation. When associated with NF1, MPNSTs tend to present at a younger age (28–36 years) than the sporadic counterpart (40–44 years).[6] The presence of divergent differentiation is highly suggestive of NF1. Fifty-seven percent of patients with MTT have NF1.[6]

Clinically, MPNST presents as a rapidly enlarging mass that may give rise to neurologic complaints. A family or personal history of NF1 is helpful in making the correct diagnosis. The proximal extremities are the most common locations of these tumors.

Grossly, MPNST is a firm tumor and may either appear pseudoencapsulated or have ill-defined margins. The tumor may grow along adjacent nerves or infiltrate nearby soft tissue. Foci of hemorrhage or necrosis may be seen. The presence of divergent differentiation is usually not readily distinguished on gross examination, with the caveat that osseous, chondroid, and mucinous elements may be apparent.

Traditionally, MPNST has been among the most challenging soft tissue tumor diagnoses to make because of the lack of standard histologic criteria. The tumor is composed of hyperchromatic spindle cells growing in a fasciculated pattern. The cytoplasm is typically light staining and indistinct. The overall architecture may be either diffuse or arranged in alternating hypocellular and densely cellular areas. High-grade tumors usually contain necrosis and increased mitotic activity (Figure 1).

Accepted for publication July 7, 2006.

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The authors have no relevant financial interest in the products or companies described in this article.

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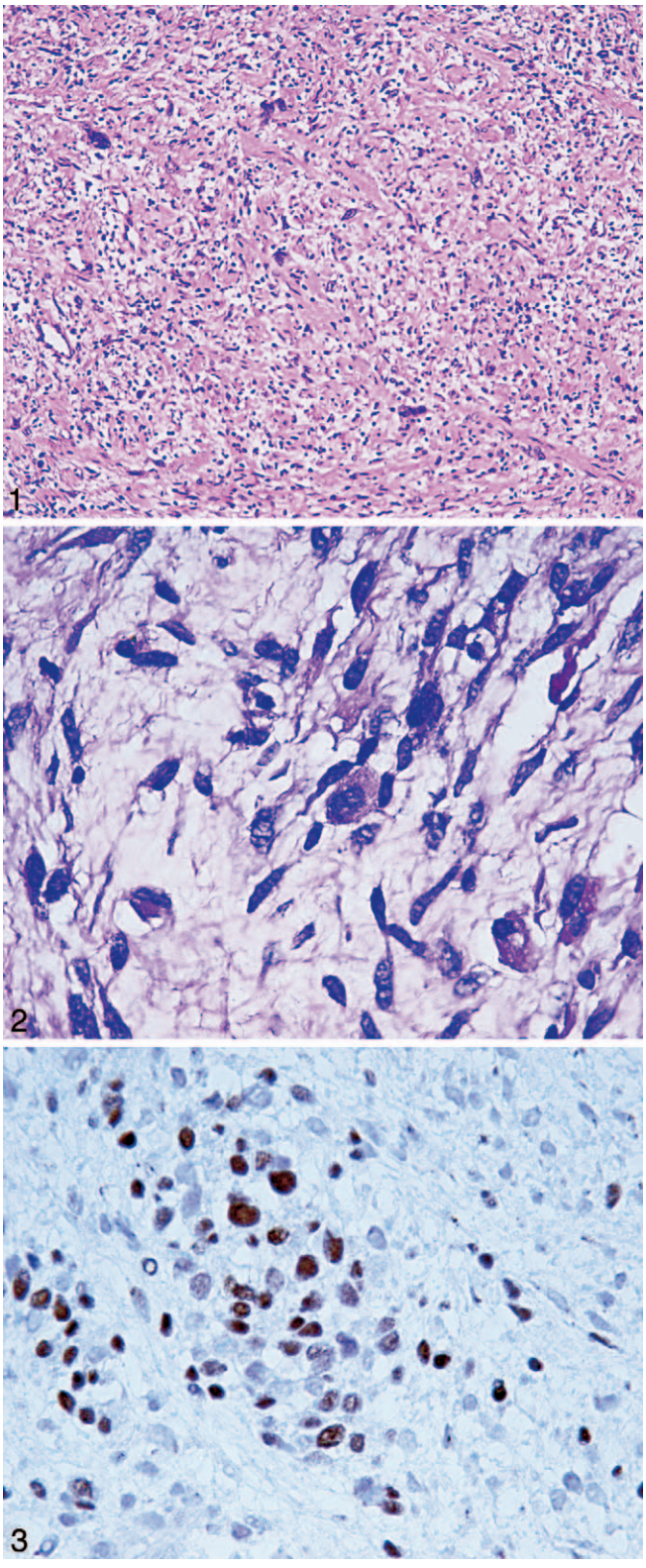

Figure 1. *Malignant peripheral nerve sheath tumor. Malignant spindle cells with marked pleomorphism and fasciculated architecture are seen (hematoxylin-eosin, original magnification ×100).*

Figure 2. *Medium-power view of a malignant peripheral nerve sheath tumor with rhabdomyosarcomatous differentiation. Round cells with eosinophilic cytoplasm morphologically consistent with rhabdoid differentiation are identified in a background of classic malignant peripheral nerve sheath tumor (hematoxylin-eosin, original magnification ×200).*

The capacity of MPNSTs to undergo focal mesenchymal (or even epithelial) differentiation is well known. Epithelial areas may be histologically benign; however, mesenchymal differentiation is sarcomatous in nature and histologically malignant.[7] Rhabdomyosarcoma (MTT) is the most frequently encountered example of divergent differentiation in MPNST. Malignant triton tumors are composed of a stroma typical of MPNST, with the added feature of rhabdomyoblasts, which usually appear round with eosinophilic cytoplasm. Cross-striations may be evident on light microscopy, and sarcomeres may be demonstrated ultrastructurally. Rhabdomyosarcomatous elements should not be confused with adjacent benign mesenchymal tissues that have been invaded. The frequency of rhabdomyoblasts is quite uneven with variable cellular distribution even within the same tumor. Additional mesenchymal or epithelial areas (pluridirectional differentiation) may be seen in 15% of MTTs (Figure 2).[7]

Immunohistochemically, S100 protein is positive in 50% to 90% of MPNSTs, with Leu-7 and myelin basic protein positivity being useful adjuncts.[5] S100 staining is focal and only present in a minority of the cells. The morphologic suspicion of rhabdoid/skeletal muscle differentiation may be confirmed with positive staining with desmin, myogenic differentiation 1, muscle-specific actin, and myogenin (Figure 3).

The capacity for divergent differentiation combined with the existence of multiple histologic variants of usual MPNST complicates the differential diagnosis. Malignant peripheral nerve sheath tumor is one of the most histologically variable soft tissue tumors, and prudent use of immunohistochemistry is essential in making a correct diagnosis. The fasciculated, spindle cell growth pattern may cause confusion with leiomyosarcoma, fibrosarcoma, or monophasic synovial sarcoma. In addition, low-grade MPNST must be distinguished from neurofibroma and cellular schwannoma. Leiomyosarcoma may be identified by the presence of blunt-ended ''cigar-shaped'' nuclei and positive immunohistochemical staining for smooth muscle actin. Fibrosarcoma may appear nearly identical to MPNST on hematoxylin-eosin–stained sections, although negativity for S100 and Leu-7 should help distinguish it from MPNST. Both fibrosarcoma and monophasic synovial sarcoma have a more uniform cellular arrangement. Epithelial membrane antigen is positive in 50% of monophasic synovial sarcomas.[5] Cytokeratin is also usually positive in monophasic synovial sarcoma. Unless areas of glandular differentiation are present, MPNSTs should be epithelial membrane antigen and cytokeratin negative. S100 is reported to be positive in up to 25% of monophasic synovial sarcomas.[5] Accordingly, one should be careful utilizing this marker in differentiating MPNST from these tumors. An additional diagnostic consideration that deserves discussion is melanoma. Strong and diffuse staining with S100, positivity for melanoma markers such as HMB-45, a higher degree of pleomorphism (usually), and nuclear pseudoinclusions should allow one to avoid a misdiagnosis.

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Figure 3. *Positive nuclear immunohistochemical staining with Myo D1, a nuclear transcriptional regulatory protein expressed early in skeletal muscle, is noted in rhabdomyoblastic cells in malignant peripheral nerve sheath tumor (original magnification ×200).*

As previously mentioned, the distinction among neurofibroma, cellular schwannoma, and low-grade MPNST is a difficult one, and firm criteria are not available. Some authors recommend a 3-tiered system representing a spectrum from benign to malignant and composed of neurofibroma, neurofibroma with atypical features, and low-grade MPNST arising in a neurofibroma. It is suggested that the presence of low levels of mitotic activity and generalized nuclear atypia are what differentiate low-grade MPNST from neurofibroma with atypical features. Some atypia in the absence of pronounced cell crowding is acceptable even within conventional neurofibromas.[5] Other authors, while also advocating the differentiation of conventional neurofibroma from atypical neurofibroma and low-grade MPNST, suggest that cell crowding, hyperchromasia, and nuclear enlargement are the minimum criteria necessary for a diagnosis of low-grade MPNST, with mitotic activity alone being insufficient evidence for a diagnosis of malignancy.[7] Cellular schwannoma is strongly and diffusely S100 positive, differentiating it from MPNST, which has only focal positivity.

Leiomyosarcoma and rhabdomyosarcoma are the primary confounding differential diagnoses when considering MTT. The possibility of positive staining with S100 protein in leiomyosarcoma[8] and rhabdomyosarcoma[9] further complicates the picture. Negative staining for smooth muscle actin combined with the presence of rhabdomyoblasts (striations, myoglobin reactivity) should effectively rule out leiomyosarcoma. The differentiation from embryonal or alveolar-type rhabdomyosarcoma is more problematic. It has been shown that only when the rhabdoid component of MTT resembles the pleomorphic type of rhabdomyosarcoma can positive staining for S100 be reliably interpreted as an indicator of nerve sheath differentiation.[2,10] The important point to remember is that, in this context, positive immunohistochemical staining for S100 protein does not necessarily confirm a nerve sheath tumor.

Until recently, few studies have examined the cytogenetics of MPNSTs and MTTs. Specific cytogenetic abnormalities are unrecognized, although it is known that the majority of these tumors have complex karyotypes. Recent work has identified recurring breakpoints in MPNST, including 1p, 7p22, 11q13→23, 20q13, and 22q11→13, with loss of chromosomal material being more frequent than gain.[11] Since there exists a known association between MPNST and NF1, the NF1 gene on the long arm of chromosome 17 (17q) is an obvious area of interest. Benign and malignant tumors in NF1 patients have been examined, and chromosome 17 losses or deletions are often present in MPNST. Surprisingly, deletions on the short arm of chromosome 17 (17p) are the most common genetic abnormality identified. Menon et al[12] proposed that the most likely target of these deletions is the p53 gene.[12] Later studies have examined MPNSTs arising within neurofibromas and have identified immunoreactivity for p53 in malignant, but not adjacent benign, areas.[13] Although p53 expression has been associated with malignant transformation in a number of studies, it has also been found to be absent in most low-grade MPNSTs and more frequently expressed in NF1-associated high-grade MPNSTs than in non-NF1 (sporadic) MPNSTs.[14] Absence of the *p53* gene (*TP53*) in animal models has been shown to result in the spontaneous development of MPNSTs, further implicating the gene in malignant transformation.[15]

Few cytogenetic studies specific to MTTs have been performed. A breakpoint involving 11p15 (the region of the myogenic differentiation 1 gene) has been identified in one reported case of MTT arising in a patient with NF1.[16] The myogenic differentiation 1 gene is normally expressed in rhabdomyosarcoma but not in conventional MPNST, implicating it as a potential contributor to rhabdomyoblastic differentiation in MTT. Amplification of *c-myc* has also been implied or observed in MTT, a finding that may explain the more aggressive behavior of MTT as compared to conventional MPNST.[16,17]

The treatment of MTT is identical to that for MPNST and is primarily surgical. A unique case was recently reported in which recurrent MTT was found to express retinoic acid receptors α and γ. The patient was treated experimentally with isotretinoin and interferon-α for 1 year, with no evidence of recurrence for more than 3 years.[18]

The prognosis for MPNST is poor, with death occurring in 63%, usually within 2 years of diagnosis.[2] Malignant triton tumors behave more aggressively than classic MPNSTs do, with crude 2-year and 5-year survival rates of 15% and 11%, respectively.[2] By way of comparison, the crude 2-year and 5-year survival rates for usual MPNST are reported to be 57% and 39%, respectively.[19]

In summary, MPNST should be in the differential diagnosis when evaluating neural tumors in young to middle-aged patients, particularly if they have NF1. The capacity for mesenchymal or epithelial differentiation within these tumors exists, with rhabdomyosarcomatous differentiation the most commonly encountered example. The diagnosis of MTT confers a more sinister prognosis than usual MPNST. Immunohistochemistry is an essential tool for ruling out differential diagnostic considerations. S100 staining should be interpreted with caution because positivity does not necessarily indicate nerve sheath differentiation. Close attention to the clinical history, with thorough consideration of other entities within the differential diagnosis, is essential.

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