Malignant Peripheral Nerve Sheath Tumor

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KEYWORDS

• Neurofibroma • Atypical neurofibroma • Malignant peripheral nerve sheath tumor • Neurofibromatosis • NF1

KEY POINTS

- Malignant peripheral nerve sheath tumor (MPNST) is the sixth most common soft tissue sarcoma, often arises from a neurofibroma, and in half of cases occurs in a patient with neurofibromatosis type I.
- The most accurate radiographic evaluation of MPNST uses a combination of PET along with CT or MRI.
- The pathologic diagnoses of peripheral nerve sheath tumors with atypia represent a histologic continuum, and include neurofibroma with atypical features, low-grade MPNST, and high-grade MPNST.
- Management and prognosis significantly differ between low-grade MPNST and high-grade MPNST.

INTRODUCTION TO MALIGNANT PERIPHERAL NERVE SHEATH TUMOR

MPNST is the sixth most common type of soft-tissue sarcoma, accounting for approximately 5% to 10% of cases.[1–3] Although its exact cellular origins remain unclear, most MPNSTs arise in association with a peripheral nerve and are hypothesized to be of neural crest origin.[4] Approximately 50% of all MPNST cases arise sporadically, whereas the other 50% of cases are observed in patients with neurofibromatosis

Disclosure Statement: The authors have nothing to disclose.
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Surg Oncol Clin N Am 25 (2016) 789–802
http://dx.doi.org/10.1016/j.soc.2016.05.009 **surgonc.theclinics.com**
1055-3207/16/$ – see front matter

type 1 (NF1).[5,6] NF1 (also termed von Recklinghausen disease) is an autosomal-dominant genetic disorder with high penetrance that is characterized by mutations in the *Neurofibromin 1* gene, in which patients develop both superficial and deep neurofibromas, among other tumor types.[7,8] Guidelines for the diagnosis of NF1 are summarized in **Box 1**. NF1 patients carry an estimated 8% to 13% lifetime risk of developing MPNST, and 30% of NF1-associated MPNSTs progress from a deeply situated neurofibroma.[8,9] The incidence of MPNST among NF1 patients is 1:3,500, in comparison to the incidence among the general population of 1:100,000.[6] NF1 patients are also predisposed to developing astrocytic brain tumors, pheochromocytoma, and myeloid leukemia, among a diverse array of other benign and malignant tumors.[10,11] Another main risk factor for the development of MPNST is radiation exposure. An estimated 3% to 10% of all MPNST patients have a clinical history of prior radiation exposure.[5] The latency period for radiation-associated MPNST is typically more than 15 years.[12] The median age at diagnosis among sporadic MPNST patients is 41 years of age, whereas NF1-associated MPNST patients are generally younger (mean age of 28 years).[13] Although infrequent, NF1-associated MPNSTs in childhood do occur.[14] The incidence of sporadic MPNST is approximately equal among men and women,[15] whereas NF1-associated MPNST is somewhat more common in men.[5]

In general, the clinical presentation of MPNST is typical of a soft tissue sarcoma. MPNST presents as an enlarging mass for several months. The location is most commonly near nerve roots and bundles of the extremities and the pelvis, including the sciatic nerve, brachial plexus, and sacral plexus.[15] Therefore, a majority of MPNST occur in the proximal portions of the upper and lower extremities. Symptoms include pain, paresthesia, and neurologic deficits.[16] New-onset pain in an existing neurofibroma, especially in an NF1 patient, should prompt evaluation for MPNST. Currently, the clinical standard of care for localized high-grade MPNST is surgical resection and adjuvant radiation. An estimated 40% to 65% of MPNST patients experience local recurrence and 30% to 60% develop metastasis, with the most common site primarily located in the lungs.[17–20] Although chemotherapy is administered to systemically manage metastatic MPNST, survival rates remain low.[21,22] In general, a diagnosis of MPNST carries a poor prognosis. For all patients with high-grade MPNST, overall 5-year survival rate ranges from 20% to 50% and a mortality rate of up to 75%.[1,4] Although it was previously believed that patients with NF1-associated tumors have a worse prognosis,[9] this has been disproved across multiple studies.

Box 1
Diagnostic criteria for neurofibromatosis type 1

Two or more of the following signs or factors

Six or more café au lait macules

Two or more neurofibromas or one plexiform neurofibroma

Axillary or inguinal region freckling

Optic glioma

Two or more iris hamartomas (Lisch nodules)

First-degree relative with NF1

Adapted from NIH consensus development conference statement of neurofibromatosis. Bethesda (MD): US Department of Health and Human Services; 1987.