**Case Report**

**Lymph node metastasis of malignant peripheral nerve sheath tumor in the absence of widespread disease five years after diagnosis: a rare finding**

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**Abstract:** Malignant peripheral nerve sheath tumor (MPNST) is a rare soft tissue neoplasm that accounts for less than 10 percent of all soft tissue sarcomas. These tumors can arise spontaneously or in association with a neurofibroma in patients with neurofibromatosis type I (NFI). Lymph node metastasis from MPNST is rarely seen and has only been reported in the setting of widespread metastasis. Therefore, regional lymph node dissections are not routinely performed in the management of MPNST. To our knowledge, this case is the first reported case of cutaneous MPNST metastatic to a regional lymph node in the absence of widespread disease. We report the case of a 49 year old male with a history of NFI and MPNST involving only the right elbow which was excised with clear margins. Five years later, he presented with an isolated 11.5 x 9.0 x 7.0 centimeter right axillary mass which was completely excised. Microscopic examination revealed metastatic MPNST with lymph node involvement. Although isolated lymph node metastasis from MPNST is rare, this case expands our knowledge of the clinical behavior of MPNST.

**Keywords:** Malignant peripheral nerve sheath tumor, spindle cell neoplasm, Lymph node metastasis, S-100

**Case History**

A 49 year old male with a history of neurofibromatosis Type I presented to an outside institution with a subcutaneous mass on his right elbow. The patient underwent surgical excision of the tumor. Gross examination revealed a 6.2 x 5.3 x 3.7 centimeter pink-white firm nodule. On microscopic examination, the epidermis was hyperpigmented but largely unremarkable. In the superficial dermis, there was a hypocellular spindle cell neoplasm, which was composed of bundles of wavy small spindled cells with hypochromatic nuclei, no mitotic figures, and intervening pink collagen morphologically consistent with neurofibroma (NF). Adjacent to these cells and within the deep dermis, was a markedly hypercellular, palisading spindle cell neoplasm that infiltrated the subcutaneous adipose tissue. Despite the high cellularity and mitotic activity, there was no significant cellular pleomorphism. Immunohistochemical stains revealed the neoplastic cells to be focally positive for S-100 and neuron-specific enolase (NSE) and negative for HMB-45, MART-1 and keratin stains. A diagnosis of malignant peripheral nerve sheath tumor (Grade II/III) arising in a neurofibroma was rendered (Figure 1) and confirmed by outside expert consultation. Five years later, this patient presented with a right axillary mass and underwent surgical excision. On gross examination, the specimen consisted of an 11.5 x 9.0 x 7.0 cm conglomerate of matted lymph nodes. Microscopic examination demonstrated a metastatic malignant spindle cell neoplasm within a conglomerate of lymph nodes with extensive extracapsular extension (Figure 2). This metastatic malignant spindle cell neoplasm was morphologically identical to the previous right elbow mass (Figure 3). As in the primary tumor, the axillary mass demonstrated high mitotic activity in the absence of significant pleomorphism. The malignant neoplastic cells again demonstrated focal positivity for S100 (Figure 4), NSE, and MIB-1 confirmed the high proliferative rate. As in the primary
Lymph node metastasis of peripheral nerve sheath tumor

Figure 1. Original malignant peripheral nerve sheath tumor (MPNST) is seen on the left and neurofibroma (NF) on the right.

Figure 2. Metastatic malignant peripheral nerve sheath tumor (MPNST) in a conglomerate lymph node.

Figure 3. Malignant peripheral nerve sheath tumor (MPNST). The marked hypercellularity and the high mitotic activity in the absence of significant pleomorphism are commonly seen in this tumor type.

Figure 4. The focal S-100 positivity supports the diagnosis of metastatic malignant peripheral nerve sheath tumor (MPNST).

tumor, the neoplastic cells were negative for HMB-45, MART-1, AE1/3 and CD34 stains. Thus, histomorphology and immunohistochemical profile support the diagnosis of metastatic MPNST with lymph node involvement.

Discussion

Malignant peripheral nerve sheath tumors (MPNST), otherwise known as malignant schwannoma, neurogenic sarcoma, or neurofibrosarcoma, constitute up to 10 percent of all soft tissue sarcomas. This malignant neoplasm is commonly thought to arise from Schwann cells in large peripheral nerves. The tumor can either arise sporadically, or can develop from a neurofibroma in patients with neurofibromatosis type I (NF1). Tumors which arise from a pre-existing neurofibroma are thought to represent dedifferentiation of Schwann cells[1]. In all, MPNST affects males more often than females. These tumors most commonly arise in the buttocks, thigh, brachial plexus, upper arm, and paraspinal regions. Although all MPNST behave aggressively, tumors that arise in the setting of NFI have an increased risk of local recurrence and distant metastasis. The neoplasm typically spreads via perineural direct invasion or through hematogenous routes [2]. The most common site of distant metastasis is the lung.
followed by bone and pleura [3]. Other distant sites include the brain, liver, and adrenal glands [4]. Lymph node metastasis are uncommon, occurring in less than 10% of patients, and are mainly seen in conjunction with widespread metastasis [3]. In fact, when lymph node metastasis is diagnosed, it has been recommended to rule out the differential diagnoses of metastatic desmoplastic or neurotropic melanoma [3]. Considering this, our case of malignant peripheral nerve sheath tumor with regional lymph node metastasis is quite uncommon.

Typical histologic features of MPNST include malignant spindle cells with pleomorphic nuclei, scattered mitoses and geographic necrosis. The differential diagnosis for spindle cell neoplasms with cytologic atypia includes spindle cell melanoma (SCM), monophasic synovial sarcoma (MSS), pleomorphic liposarcoma (PLS), malignant fibrous histiocytoma (MFH), and metastatic carcinoma (MC). The exclusion of SCM is of particular importance since the spindle cell and desmoplastic variants of melanoma can often have neural-like nuclear morphology. In this regard, the use of second-line melanoma immunohistochemical markers such as NSE or CD56 may also be helpful, as HMB45 and Melan-A may fail to stain melanomas with spindle cell morphology [4]. Also in the differential, synovial sarcomas are usually positive for CK7 and CK19. PLS may show at least focal typical liposarcomatous areas and scattered enlarged round to bizarre nuclei. MFH is a diagnosis of exclusion; the tumor must be sampled generously and searched for other components to rule out a dedifferentiated tumor or evidence of specific differentiation other than fibroblasts or myofibroblasts. MC will demonstrate variable reactivity to keratin stains.

Several prognostic indicators have been proposed for MPNST. Some features that are associated with a worse prognosis include tumor size greater than 5cm, history of NFI, degree of pleomorphism, and mitotic activity [5-6]. Reduced survival rates have been associated with metastasis and incomplete surgical excision, and are also influenced by tumor size and grade [4, 7]. Primary tumor size greater than 10 cm as well as tumors located outside of the extremities are associated with an increased risk of metastasis [4]. Furthermore, a recent study has shown that tumors lacking S100 positivity are associated with much higher risk of metastasis and a higher mortality rate [4]. Primary treatment for these neoplasms includes complete surgical excision. MPNST has historically been reported to be radio- and chemotherapy sensitive [6]. While radiation therapy has been shown to delay tumor recurrence, long term survival is not greatly improved [8]. In cases of metastatic disease, chemotherapy is used for palliative care or the management of unresectable tumors. However, the survival benefit of chemotherapy in the management of MPNST has not be statistically proven [8].

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