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Review Article

Malignant peripheral nerve sheath tumor: pathology and genetics ☆

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ABSTRACT

Malignant peripheral nerve sheath tumors are soft tissue neoplasms that show differentiation toward cells of the nerve sheath. They often arise from peripheral nerves or preexisting benign nerve sheath tumors and are generally high-grade neoplasms, which behave aggressively with high incidence of distant metastases. Malignant peripheral nerve sheath tumor can be histologically diverse and is difficult to diagnose because of its morphological overlap with a variety of other sarcomas and its lack of specific immunohistochemical markers or genetic profile. We review the pathology of malignant peripheral nerve sheath tumor, with reference to etiology, molecular genetics, and clinical factors.

1. Introduction

Malignant peripheral nerve sheath tumors (MPNSTs) are soft tissue neoplasms that usually arise from peripheral nerves and show variable differentiation toward one of the cellular components of the nerve sheath (Schwann cells, fibroblasts, and perineurial cells). They can occur sporadically or in patients with neurofibromatosis type 1 (NF1) and arise either *de novo* or from a preexisting neurofibroma or, rarely, schwannoma. They form a heterogeneous group of neoplasms with a range of morphology and are often aggressive tumors with a tendency to recur and metastasize. Effective targeted molecular treatments are not available, and surgical resection remains the mainstay of treatment. Because of their morphologic heterogeneity and the lack of specific immunohistochemical or molecular markers, histologic diagnosis is challenging.

Malignant peripheral nerve sheath tumors mainly affect adults with a roughly equal sex distribution, and although the age range is wide, they tend to occur at a younger mean age in patients with NF1. More rarely, MPNST can develop during childhood [1,2]. Approximately 10% of tumors are associated with previous radiation exposure, either therapeutic or environmental, and developing after a latent period [3,4]. A specific "cell of origin" is as yet unknown, although it has been postulated that they may develop from neural crest cells.

Malignant peripheral nerve sheath tumor occurs most frequently in the extremities, particularly proximally, followed by the trunk and head and neck. Most arise in major nerve trunks such as the sciatic nerve. Patients may present with a painful or rapidly enlarging mass with associated neurologic deficits. Poorer prognosis is associated with large tumors (with size varying from >5 to >7 cm in different studies) and those associated with NF1 as well as those of higher grade and with truncal location [5,6]. Other unfavorable features include a mitotic index of greater than 6/10 high-power fields and incomplete resection [6-9]. The recurrence rate is up to 40%, and approximately two-thirds metastasize, usually hematogenously to the lungs and bone. Five-year survival has varied in series from 26% to 60%, and 10-year survival is approximately 45% [5,9,10].

Radical surgery continues to be the mainstay of current management, as these tumors have limited sensitivity to chemotherapy and radiation. The role of adjuvant treatment is as yet unclear. Radiotherapy may be used to control local disease and reduce recurrence, but it appears to have little effect on long-term survival [11,12]. Chemotherapy is generally not effective, although some studies have shown that it may benefit patients with high-grade histology [13] or children with unresectable tumors [12,14]. There are currently no effective targeted therapies for MPNST, although there are currently several preclinical and clinical studies. Potential targets include the mammalian target of rapamycin (mTOR) pathway using the mTOR inhibitor rapamycin alone or in combination with AKT inhibitors, which is demonstrating promising preclinical results for treatment of MPNST [15-19]. Patients should be referred to centers with experience in treating soft tissue sarcomas and the facility to enroll patients in clinical trials [13].

Neurofibromatosis type 1 (von Recklinghausen disease) is an autosomal dominantly inherited disorder, with a diverse range of clinical signs that affects approximately 1 in 3500 newborns. It is caused by a germ line mutation causing inactivation of the *NF1* tumor suppressor gene on 17q11.2, which arises as a *de novo* mutation in approximately 50% of affected individuals. Although NF1 is completely penetrant, its range of manifestations is highly variable. The hallmark of NF1 is the presence of multiple dermal or plexiform neurofibromas, but the disease can have multiple manifestations in

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different organ systems. Abnormalities associated with NF1 include pigmented lesions (café au lait spots, Lisch nodules, and axillary freckling); bony dysplasias; and the occurrence of a variety of neoplasms such as optic gliomas, higher grade astrocytic neoplasms, and pheochromocytomas as well as learning disabilities [20]. The biallelic inactivation of the *NF1* gene through a "second hit" seems to be of crucial importance to the development of certain manifestations, such as neurofibromas and café au lait macules, in which the second hit appears to involve only 1 cell type that is subsequently clonally expanded in a discrete lesion [21].

Patients with NF1 are at higher risk for developing soft tissue sarcomas than the general population, and MPNST is the most common malignancy associated with this disorder. The lifetime risk of MPNST in NF1 is approximately 5% to 10% (compared with 0.001% in the general population) [13], with 1% to 2% of NF1 patients developing the tumor, and studies have suggested that MPNSTs associated with NF1 are associated with a significantly poorer outcome than sporadic cases. Malignant peripheral nerve sheath tumor is the leading cause of mortality in NF1. Neurofibromatosis type 1 patients with MPNST are significantly younger at diagnosis (with a peak incidence in the fourth decade) are more often males with tumors in an axial site, may have multiple neoplasms, and show both shorter survival times and times to local recurrence and metastasis [22]. Many neoplasms arise in preexisting classical or plexiform neurofibromas or in a nerve trunk. Malignant peripheral nerve sheath tumors in NF1 patients also more frequently display divergent differentiation.

Most NF1 patients carry a constitutional mutation of the *NF1* gene. Its loss, as a tumor suppressor gene, predisposes to tumor development. The protein product of *NF1*, neurofibromin, is a ubiquitous Ras GTPase-activating protein and is a negative regulator of the *Ras* proto-oncogene and its signal transduction pathway [23]. RAS proteins (HRAS, NRAS, and KRAS) are guanosine-binding proteins that act as molecular switches controlling and regulating intracellular signaling networks, including those involved in proliferation, differentiation, migration, and apoptosis. Neurofibromatosis type 1 is considered one of the "Rasopathies," and *NF1* gene deficiency leads to Ras hyperactivation, and the increase in Ras signaling to its downstream effectors leads to the disruption of multiple pathways including Ras/mitogen-activated protein kinase (MAPK)/ERK and Akt/mTOR. The activation profiles of the AKT/mTOR and MAPK pathways in MPNSTs still remain to be better elucidated.

2. Neurofibroma

Most tumors of the human peripheral nervous system derive from Schwann cells or their precursors. Neurofibromas are benign peripheral nerve tumors that occur either sporadically or in approximately 10% are associated with NF1. The primary neoplastic cellular component of neurofibroma is the Schwann cell [24], but neurofibromas also contain a mixture of nonneoplastic peripheral nerve components, including axons, fibroblasts, perineurial cells, and inflammatory cells such as mast cells [25]. The types of neurofibroma specific for NF1 are multiple localized cutaneous neurofibroma, plexiform neurofibroma, and massive soft tissue neurofibroma [26]. However, only plexiform and localized intraneural neurofibromas are significant precursors of MPNST [26]. Although all neurofibromas carry a risk of transformation to MPNST, those that transform are usually deeply sited, and the risk is much greater in plexiform neurofibromas. Plexiform neurofibromas usually present in early childhood and are multinodular lesions involving multiple nerves or nerve branches. These generally affect small nerves but can affect the entire extremity, giving rise to "elephantiasis neuromatosa." The risk of transformation of plexiform neurofibroma to MPNST is approximately 5% [6], and the evidence from clinical studies suggests that most MPNSTs in patients with NF1 develop from preexisting plexiform neurofibromas [27]. Atypical neurofibromas show foci of increased cellularity, with interspersed enlarged and hyperchromatic nuclei. These tumors may be precursors of MPNST and are usually seen in patients with NF1. Atypical neurofibroma and low-grade MPNST represent a morphologic continuum, so differentiating the two is difficult, but low-grade MPNST shows more generalized nuclear atypia and increased cellularity with low levels of mitotic activity [28,29]. Neurofibromas can have features of "ancient change" similar to that seen in schwannomas, with scattered cells showing enlarged and hyperchromatic nuclei with smudgy chromatin and degenerative-type atypia. These, however, lack fascicular growth pattern, increased cellularity, or mitotic activity [25], and these features are insufficient for atypical neurofibroma. Weiss and Goldblum [28] suggest that, if there is no mitotic activity, low-grade MPNST can be diagnosed if cellularity (with almost back-to-back cells forming sheets and fascicles) and atypia are marked. Schwannoma can also rarely undergo malignant transformation [30], usually to epithelioid MPNST, although occasionally to angiosarcoma [31-33]. Malignant peripheral nerve sheath tumor has also been reported to arise from traumatic neuroma [34].

3. Genetics, including transformation from neurofibroma

Malignant peripheral nerve sheath tumors have complex karyotypes, with multiple numeric and structural abnormalities. No specific balanced gene rearrangements have been identified. The most frequent gene alterations include loss of *NF1* on 17q11 and of *p53* on 17q13, and these can include inactivation of the *NF1* tumor suppressor gene, both in sporadic cases and NF1 patients. The molecular basis for transformation of neurofibroma to MPNST is still poorly understood. Gene expression analyses of both tumors have shown a major trend in malignant transformation consisting of loss of expression of several genes, rather than marked increase in gene expression [35]. Tumorigenesis in NF1 is thought to require the somatic loss of the second *NF1* allele (biallelic *NF1* gene inactivation) [36], and inactivation of both alleles has been shown in both neurofibromas and MPNST [37,38] compared with heterozygosity within nonneoplastic cells. This loss of heterozygosity in the progenitor cell, which may be a Schwann cell or its precursor, is combined with haploinsufficiency in multiple supporting cells [15]. In addition to loss of *NF1*, for malignant transformation to arise, it is thought that there must be a multistep accumulation of additional mutations of multiple tumor suppressor, cell cycle, and signaling regulation genes including *CDKN2A*, *P53*, *RB1*, *SOX9*, and *MET* with resulting abnormalities of their respective signal cascades [15] and receptor tyrosine kinase amplification (eg, epidermal growth factor receptor) [36,38-40]. Although there are no defined molecular signatures for MPNST development [36], most show a gene expression signature indicating p53 inactivation [35] as well as a relative down-regulation of miR-34a compared with neurofibromas. Relatively few genes are expressed at higher levels in MPNSTs and include those involved in cell proliferation and tumor metastasis [35].

Molecular determinants of prognosis are not as yet established, but studies have shown that, for NF1-associated patients, there was a clear association between nuclear expression of p53 and poor survival [41]. Recent array comparative genomic hybridization-based studies have shown highly complex copy number alterations, with 4 regions of copy number gain associated with poor patient survival. These regions include candidate genes *SOX5* (12p12.1), *NOL1* and *MLF2* (12p13.31), *FOXM1* and *FKBP1* (12p13.33), and *CDK4* and *TSPAN31* (12q14.1). *CDK4* gain/amplification and increased FOXM1 protein expression were found to be the most significant independent predictors for poor survival in MPNST patients [42]. p-AKT, p-mTOR, and p-S6RP expressions have been associated with poor prognosis in MPNST, and mTOR inhibition by everolimus *in vitro* has shown antitumor activity in MPNST cell lines. Mammalian target of rapamycin inhibition is a potential treatment option for both NF1-related and sporadic MPNST [43].