

Solid Tumour Section

Mini Review

Nervous system: Peripheral nerve sheath tumors

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Classification

A peripheral nerve sheath tumor (PNST) is a neoplasm arising from a peripheral nerve or showing nerve sheath differentiation. PNSTs may be subdivided into benign and malignant (MPNST) variants. Several distinct benign subtypes have been recognized, including schwannoma (neurilemoma, neurinoma), neurofibroma, and perineurioma.

Clinics and pathology

Etiology

The etiology of PNSTs is usually unknown. However, several hereditary disorders are known to predispose to benign and malignant PNSTs, notably neurofibromatosis type 1 (NF1) and neurofibromatosis type 2 (NF2), both of which are inherited in an autosomal dominant fashion. NF1 (also known as von Recklinghausen disease) is caused by mutations in the NF1 gene on chromosome 17 and is characterized by several phenotypic features including multiple neurofibromas and MPNSTs. The incidence of MPNST is in general rare, but half of all cases arise in NF1 patients. NF2, caused by mutations in the NF2 gene on chromosome 22, predisposes to schwannomas, predominantly affecting the spine and the intracranial nerves.

Epidemiology

All ages and both sexes may be affected by PNSTs. Sporadic MPNSTs are most common between 40 and 50 years of age, while those occurring in the setting of NF1 are diagnosed some 10 years earlier. In total, MPNSTs account for 5-10% of all soft tissue sarcomas.

Pathology

Schwannomas are encapsulated spindle cell tumors with distinct Antoni A and B components, hyaline vessel walls, and nuclear palisading. Tumor cells are strongly immunopositive for the S-100 protein.

Neurofibromas are unencapsulated tumors composed of spindle cells dispersed in fibromyxoid stroma. The proportion of S-100 positive cells is variable.

Perineuriomas may arise in soft tissues or within nerves, and are composed of cells with elongated bipolar cytoplasmic processes frequently arranged in whorls or a storiform pattern. The neoplastic cells express vimentin and epithelial membrane antigen (EMA), but are negative for S-100 protein, desmin, muscle-specific actin, and CD34.

MPNSTs typically are characterized by the presence of pale spindle cells often arranged in fascicles with alternating cellular and more myxoid areas. The S-100 protein is expressed in 50-70% of the tumors, and the majority of cases are immunopositive for TP53. Most MPNSTs arise from Schwann cells, but the possibility remains that some arise from nerve sheath cells other than the Schwann cells, and approximately two-thirds of all MPNSTs are associated with neurofibromas.

Prognosis

Benign PNSTs rarely recur after surgery. MPNST, on the other hand, is often a highly aggressive tumor, and more than 60% of the patients die of the disease.

Cytogenetics

Cytogenetics Morphological

Schwannomas: Approximately 75 cases with clonal chromosome aberrations have been reported.

Irrespective of site of origin, these tumors almost always display a near-diploid karyotype, with loss of chromosome 22 material, either through loss of the entire chromosome 22 or through partial deletions of the long arm, as the most common (about half of the cases) abnormality. Other recurrent abnormalities include, in decreasing order of frequency, loss of a sex chromosome, -17, -15, and +7.

Neurofibromas: Only five cases with clonal chromosome abnormalities have been reported, and no recurrent abnormality has been detected among them. All had, however, near-diploid karyotypes, and one case displayed monosomy 22.

Perineuriomas: There is a dearth of information on perineuriomas, but from the few cases that have been analyzed, it seems as if loss of chromosome 22 sequences is a prominent feature, indicating that they are pathogenetically related to schwannomas.

MPNSTs: Less than 75 cases with clonal chromosome aberration have been reported. The majority of cases displays complex karyotypes, often with a chromosome number in the triploid or tetraploid range. No specific balanced rearrangement has been detected among them. Frequently involved breakpoints (at least 10% of the cases) include 1p11, 5p15, 7p22, 9p11, 11q13, 17p11, 17q11, 17q21, 20q13, and 22q11. Frequent (at least 20% of the cases) chromosomal imbalances include loss of 1p21-p36, 3p21-p23, 5p15, 6q23-q27, 7p22, 9p12-p24, 10p, 11p, 11q13-q25, 12p13, 12q22-q24, 13p, 15p, chromosomes 16 and 17, 19p, 20q13, and chromosomes 22 and X, and gain of chromosome 7. No clear difference in karyotypic profile between sporadic cases and NF1-associated MPNSTs has been detected.

Cytogenetic-morphologic correlations

Schwannoma: No association between karyotypic features and patient age, tumor size, or site of tumor origin has been detected.

MPNST: Preliminary data indicate that the presence of a triploid or tetraploid clone is associated with large-sized tumors, high-grade tumors, and shorter overall survival.

Molecular cytogenetic - clinical correlation MPNST: One study has reported poor overall patient survival associated with simultaneous gain of 17q and 7p.

Cytogenetics Molecular

Schwannoma: Comparative genomic hybridization (CGH) analysis of a limited number of sporadic and NF2-associated schwannomas has shown that loss of 22q sequences is the most frequent imbalance.

MPNST: About 50 cases have been investigated by CGH. In contrast to the imbalance maps derived from cytogenetic analyses, the CGH data indicate that gain of distal 17q and loss of 13q14-q21 are frequent (approximately half of the cases) in MPNST. Additional frequent changes reported are gain of 5p, 7, 8q and loss of 9p sequences.

Genes involved and proteins

Note: Molecular genetic findings

Schwannoma: The frequent finding of deletions at 22q suggests that this chromosome arm harbors one or more tumor suppressor loci of importance for schwannoma development. Focussing on the NF2 locus, loss of this tumor suppressor gene has been demonstrated in one third to half of all schwannomas investigated. The importance of this gene in schwannomas is further supported by the finding of biallelic inactivating mutations in up to two thirds of the cases.

Neurofibroma: Biallelic inactivation of the NF1 gene in 17q has been demonstrated.

MPNST: The basis for MPNST occurring in the setting of NF1 is presumed to be biallelic inactivation of the NF1 gene. Indeed, allelic imbalance at the NF1 locus in 17q is commonly (20-50% of the cases) detected in sporadic as well as NF1-associated MPNSTs. Due to the large size of this gene, however, it has been difficult to identify the mutation in the non-deleted copy in but a few cases. From studies of neurofibromas in NF1 patients, showing frequent deletion of the wild-type allele, it is obvious that NF1 inactivation is not sufficient for malignant transformation. Molecular genetic investigations aiming at disclosing mechanisms of importance for tumor progression have revealed that MPNSTs often display disruption of the RB1 pathway. Thus, the CDKN2A locus in 9p21 often displays loss of heterozygosity, and the gene itself is homozygously deleted or otherwise rendered functionally inactive. Also the CDKN2B and RB1 tumor suppressor genes may be inactivated in a subset of MPNSTs. Alternatively, dominantly acting genes in the RB1 pathway - CDK4, MDM2, and CCND2 - may be overexpressed or amplified. In a study of 12 MPNSTs, changes in one or more of these dominantly or recessively acting genes were found in 11 cases. The TP53 gene, on the other hand, seems to be biallelically affected in only a small proportion of MPNSTs.

To be noted

Note: Mouse model

Mice with heterozygous Nf1 germline mutation do not develop MPNST, and germline homozygosity results in embryonic lethality. However, mice with heterozygous germline mutations of both Nf1 and Tp53 develop MPNST. This animal model and the fact that biallelic inactivation of TP53 is rare in human MPNST suggest that other components of the TP53 pathway are targets for transformation of a neurofibroma into an MPNST.

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