

Ewing's Sarcoma / PNET: A Histopathological Review

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Abstract

Ewing's sarcomas (EWS) / Peripheral primitive neuroectodermal tumours (PNET) are small round cell tumours occurring in bone and soft tissues, characterized as a group by the presence of the typical translocation t (11; 22) (q24; q12) and its variants. Diagnosis requires histopathological examination, immunohistochemistry and cytogenetics. There is a spectrum of histological appearance, which reflects the degree of neuroectodermal differentiation in these tumours posing diagnostic difficulties. The current concepts in diagnosing these tumours and the clinical impact of neural differentiation are discussed.

INTRODUCTION

Primitive neuroectodermal tumour is a malignant neoplasm that originates from the cells of the primitive neural crest. It was first coined for a group of embryonal tumors located in the central nervous system (cPNET). More recently, the PNET concept has been expanded to include histologically similar, peripherally located tumours, referred to as peripheral PNET's [pPNET's]¹. Among the cPNET's are medulloblastoma, pineoblastoma, cerebral neuroblastoma, ependymblastoma, medulloepithelioma, primary rhabdomyosarcoma, and atypical teratoid/rhabdoid tumour². The pPNET is part of the Ewing's sarcoma family of tumours, which includes Ewing's sarcoma of bone, extraosseous Ewing's tumour and primitive neuroectodermal tumour³. Various synonyms including peripheral neuroepithelioma, peripheral neuroblastoma, and Askin tumour have been used to describe peripherally occurring primitive neuroectodermal tumours⁴.

DISCUSSION

Ewing's sarcoma (EWS) / peripheral primitive neuroectodermal tumour (PNET) are small round cell tumours occurring in bone and soft tissues, characterized as a group by the presence of the typical translocation t (11; 22) (q24; q12) and its variants⁵. EWS/PNET's are most common in children and young adults. The tumours usually involve bone or soft tissue within the limbs. These tumours have also been described in the mandible, kidney, parotid gland, chest wall, ovary, rectum, gall bladder, retroperitoneal cavity, myocardium^{6,7,8,9,10,11,12,13,14,15}. The tumours are rare and aggressive, with a tendency to recur and to metastasize

especially to lungs, bone marrow, brain and lymph nodes¹⁶.

Histological differential diagnosis of EWS/PNET includes rhabdomyosarcoma, neuroblastoma (NBT) and lymphomas. EWS/PNET's are difficult to distinguish from other tumours on the basis of cytology and histology alone¹. Diagnosis requires histopathological examination, immunohistochemistry and cytogenetics. Microscopically, EWS/PNET are composed of uniform small round cells with round nuclei containing fine chromatin, scanty clear or eosinophilic cytoplasm, and indistinct cytoplasmic membranes. The term Ewing's sarcoma has been used for those tumours that lack evidence of neuroectodermal differentiation, whereas, the term PNET has been employed for tumours that demonstrate neuroectodermal features¹⁷.

Neural differentiation in EWS/PNET tumours can be assessed at the histological, immunohistochemical, and electron microscopic level. The identification of a point of transition between EWS/PNET in a continuous spectrum of neural differentiation is still a matter of debate¹⁸.

Histologically, there is a spectrum of appearances which reflects the degree of neuroectodermal differentiation. Tumours at the poorly differentiated (Ewing's) end of spectrum have scanty, pale cytoplasm and round to ovoid open nuclei with finely distributed chromatin pattern. At the opposite end of the spectrum the cells may have somewhat eosinophilic cytoplasm and the chromatin pattern may be coarser with more frequent nucleoli¹⁹. Mitotic figures are common in PNET, as are necrosis and endothelial hyperplasia²⁰. A further aid in the differential diagnosis is

provided by the presence of Homer-Wright rosettes in PNET's²¹.

EWS/PNET's are characterized by immunoreactivity for the surface antigen CD99/ MIC2, which is expressed in up to 97% of cases¹⁸. The demonstration of immunoreaction with the p30/32 MIC2 antigen (CD99) is however not confined to PNET/EWS. Studies have also demonstrated positive staining to CD99 in acute lymphoblastic lymphoma, related leukaemias, alveolar rhabdomyosarcoma and granulocytic sarcoma (acute myeloid leukaemia)²³.

The EWS/PNET spectrum shows immunohistochemical evidence of neuroectodermal differentiation by positivity for antigens such as NSE, PGP 9.5, neurofilament, Leu-7 and synaptophysin¹⁹. A positivity of these markers is more commonly seen in PNET's. Neurofilament expression appears to be a more specific marker, but its frequency is generally low in this family of tumours¹⁸.

Electron Microscopy Has Been Used To Study The Cells Of EWS/PNET In Detail.

Neurosecretory granules and neurite-like cytoplasmic processes are features of neuronal differentiation that can be recognized in PNET/EWS at the ultrastructural level¹⁸. There is a comparable spectrum of differentiation ranging from the traditional paucity of organelles and copious glycogen at the Ewing's end, through the acquisition of microtubule and neurosecretory granules, to the well formed neuritic processes at the PNET end¹⁹.

If both immunohistochemistry and electron microscopy are used in association to assess neural differentiation, then the number of well-differentiated tumours recognised would be higher than if only one of the two techniques is used¹⁸.

EWS/PNET's are capable of epithelial differentiation; with consequent diagnostic difficulties. In the presence of cytokeratin expression, a poorly differentiated carcinoma should be considered. However cytokeratin expression is present in as many as 20% of EWS/PNET in either a diffuse or focal pattern²³. A study conducted on 12 well-documented EWS/PNET's that stained strongly for pankeratin by immunohistochemistry showed that keratin-positive EWS/PNET's have evidence of epithelial differentiation ultrastructurally, and may possibly represent a more aggressive subset of the EWS/PNET group of tumours²⁴.

Cytogenetic Studies In EWS/PNET Reveal A Typical EWS-FLI-1 Fusion Transcript. PNET and EWS Carry Identical

Chromosomal Translocations – T (11; 22) (Q24; Q12), Which Results In The Fusion Of The Fli-1 Gene On 11q24 And The Ews Gene On 22q12. This Is The Most Specific Feature For Diagnosis Of Pnet/Ews Tumours And Can Be Readily Detected Using The Reverse Transcriptase Polymerase Chain Reaction (Rt-Pcr)²⁴.

Different histopathological appearance is an important prognostic variable. There have been conflicting results in the literature concerning the impact of neural differentiation on the prognosis. The results of a study done in 2001, do not demonstrate a relationship between histological features and the prognosis. This does not support the concept that tumours with more extensive neural differentiation may carry a poorer prognosis²⁵. In another study the patients with tumour expression of one neural marker had 57% 3-year EFS, whereas those with two or more neural markers had 48% 3-year EFS (P = .94)²⁶. A study on 63 patients by Parham et al, showed neural differentiation had no prognostic significance²⁷.

CONCLUSION

Ewing's sarcomas (EWS) and peripheral primitive neuroectodermal tumours (PNET) are small round cell tumours that belong to the Ewing's family of tumours. Diagnosis requires histopathological examination, immunohistochemistry and cytogenetics. There is a spectrum of histological appearance, which reflects the degree of neuroectodermal differentiation in these tumours posing diagnostic difficulties. The prognostic significance of neural differentiation in EWS/PNET remains a controversial issue.

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