Sarcoma Research - International

Austin Publishing Group

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Mini Review

Ewing Family of Tumors (Ewing Sarcoma/Peripheral Neuroectodermal Tumor)

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Received: August 26, 2014; **Accepted:** October 03, 2014; **Published:** October 07, 2014

Abstract

Extraskeletal Ewing Sarcoma (ES) and Peripheral Primitive Neuroectodermal Tumor (PNET) are considered to represent two ends of the same spectrum, and hence appropriately named Ewing Family of Tumors (EFT). These tumors are characterized by *EWSR1* gene rearrangement, most often as a consequence of a reciprocal t(11;22)(q24;q12). There is no clinical or therapeutic value in attempting to separate ES and PNET, and there is no correlation between the degree of neuroectodermal differentiation and prognosis.

Keywords: Ewing Sarcoma; Immunohistochemical; Neuroectodermal; Cytokeratin; Adamantinoma; Neuroblastoma; Chondrosarcoma; Rhabdomyosarcoma

Introduction

Ewing family of tumors includes extraskeletal Ewing Sarcoma (ES) and Peripheralprimitive Neuroectodermal Tumor (PNET). It is characterized by its own distinctive clinical and pathologic features. These neoplasms are heterogeneous, and of uncertain histogenesis because we have no known normal tissue counterpart. Genetic aberrations have been found in virtually all of these tumors, contributing to the pathogenesis of the tumor, or occurring secondarily later in tumor development and progression. Ewing initially described the tumor as a round cell neoplasm involving the bone of an adolescent, calling it a diffuse endothelioma of bone [1]. The first case of extraskeletal ES was described by Angervall and Enzinger [2]. Seemayer et al. described a soft tissue tumor arising unrelated to structures of the peripheral or sympathetic nervous system, so-called PNET [3]. Immunohistochemical studies, cytogenetic and molecular testing have now established that ES and PNET represent ends of the morphologic spectrum, and therefore are best categorized as Ewing Family of Tumors (EFT), since almost all EFT demonstrate translocation involving *EWSR1*gene at 22q12 [4,5].

Clinical features

EFT typically affects adolescents or young adults, with a median age of 30 years. There is a slight male predilection, and the incidence is higher in Caucasians [6]. Although anybody site could be involved; the lesion is most common in the deep soft tissues of the extremities, with a predilection for upper half of the lower and upper extremities. Clinically, EFT grows rapidly and presents as a deeply located solitary mass. Approximately one third cases are associated with pain, particularly when they are in the vicinity of peripheral nerves.

Pathologic findings

Grossly, the tumor has a variegated appearance with a grey yellow or tan cut surface showing areas of necrosis, cystic degeneration or hemorrhage of varying extents.

These tumors are heterogeneous and can show a variety of histologic findings. The typical features of ES include cellular neoplasm composed of diffuse and monotonous round cells that are solidly packed. The individual cells are round to oval with distinct nuclear membrane, fine nuclear chromatin, with inconspicuous nucleoli. In the majority of cases, the cytoplasm appears vacuolated due to the presence of intra-cellular glycogen, and in other cases the cytoplasm may appear scanty and pale staining. The nuclei may appear indented if there is abundant cytoplasmic glycogen. Mitotic figures are rare. In some cases, a subset of cells may appear large sized with irregular nuclear membranes, high nuclear to cytoplasmic ratio and prominent nucleoli, representing a large cell or atypical variant of ES [7,8]. Areas of cystic degeneration and/or necrosis can be seen. Areas of hemorrhage within the tumor may cause hemorrhagic zones resembling a vascular neoplasm. A wide morphologic spectrum has been recognized, and continues to expand; this includes pseudo-alveolar pattern, cytokeratin positive tumors, and adamantinoma like cases [7,9,10].

The typical PNET cases are characterized by diffuse sheets of small round to oval cells with distinct nuclear membranes, find powdery chromatin and occasional prominent nucleoli. Homer Wright rosettes caused by elongated hair-like cytoplasmic extensions forming a central solid core of neurofibrillary material are a distinct morphologic finding. Cartilaginous or osseous differentiation may be seen in rare cases [11]. Immunohistochemical evidence of neural differentiation is required to make a diagnosis of PNET, irrespective of the presence or absence of rosettes. EFT is considered a more appropriate terminology since recent studies have failed to establish any clinical or therapeutic difference between ES and PNET.

CD99 was described, in the early 1990s, as a highly sensitive marker for EFT [7]. However, given the poor specificity; it is always advisable to employ CD99 as part of a panel of immunostains. Cases of EFT with typical morphologic findings, which are CD99 negative, should be confirmed by cytogenetic or molecular testing. Majority of the EFT, more so with PNET and less in ES, also show immunoreactivity for neuronal markers such as synaptophysin, Neuron Specific Enolase (NSE), PGP9.5, CD57, and S100 protein [12]. Broad spectrum cytokeratins such as pancytokeratin AE1/AE3 have shown positivity in up to 25% of ES; however, these do not stain

Citation: Sangle NA. Ewing Family of Tumors (Ewing Sarcoma/Peripheral Neuroectodermal Tumor). Sarcoma Res Int. 2014;1(1): 2.

with high molecular weight cytokeratins [7]. The adamantinoma-like histologic variant typically shows strong immunoreactivity for AE1/AE3 [7]. Polyclonal antibodies to FLI1 protein demonstrate nuclear positivity in 71-84% cases of ES/PNET [13].

A defining feature of the EFT includes *EWSR1* gene translocations with one of several members of the *ETS* family of transcription factors [14]. Majority of the cases show t (11;22)(q24;q12), which results in fusion of 3' end of the *FLI1* gene on 11q24 with the 5' end of the *EWSR1* gene on 22q12; the second most common translocation partner for *ESWR1* being *ERG* [14]. Other, less common translocation partners include *ETV4* at 17q12, *FEV* at 2q33, and *ETV1* at 7p22. The genetic fusions can be detected by florescent in situ hybridization (FISH) or reverse transcriptase polymerase chain reaction (RT-PCR) techniques. FISH has a sensitivity and specificity of 91% and 100% respectively, while that for RT-PCR is only 59% and 85% respectively [15].

Differential diagnosis

The morphologic appearance of EFT is that of a small blue round cell tumor, which typically includes several different morphologically similar appearing neoplasms. Neuroblastoma is a differential diagnostic consideration, particularly in PNET cases due to the presence of rosettes. Neuroblastoma affects patients of much younger age group, generally less than 5 years of age. Laboratory testing reveals elevated urinary catecholamine metabolites in majority of the patients. Although the morphologic findings can be largely similar, the absence of CD99 immunoreactivity, and the positivity for NB-84 [16] are distinct immunophenotypic differences. Also, cytogenetic studies do not reveal evidence of *ESWR1* aberrations. Non-Hodgkin lymphoma can be excluded by the presence of immunoreactivity for CD45 or T- and B-lymphoid cell markers. Caution should be exercised when using CD99 in isolation since T-lymphoblastic lymphomas are often intensely positive for it. Rhabdomyosarcoma, particularly alveolar rhabdomyosarcoma could be a differential diagnostic consideration based on morphology; however, immunoreactivity for myogenic markers including myogenin and myoD1 can easily distinguish this entity from EFT. Desmoplastic small round cell tumor, another differential diagnostic consideration, shows a diverse immunohistochemical profile with coexpression for desmin, vimentin, cytokeratin, with majority of cases showing immunoreactivity for WT1 (c-terminus). Merkel cell carcinomas show distinct punctate or globular immunoreactivity for low molecular weight cytokeratins, particularly CK20 which is generally absent in EFT. Other rare neoplasms with small blue round cell morphology, such as mesenchymal chondrosarcoma, small cell osteosarcoma, poorly differentiated synovial sarcoma may be considered in the differential; however, these can be distinguished from EFT based on their distinct immunophenotypic expression and cytogenetic aberrancies.

Clinical Behavior and Therapy

With the progress of modern therapy, the prognosis for patients with extraskeletal Ewing sarcoma has significantly improved. In patients with localized disease, combinations of surgery and/or radiotherapy and systemic chemotherapy have been associated with high disease-free survival rates [17]. The prognosis for patients with the presence of recurrence, or metastatic disease at the time of clinical presentation, continues to remain poor. Several clinical trials through the Children's Oncology Group (COG) and European Cooperative Groups are ongoing. Potential targeted therapies, based on the cytogenetic aberrations have been proposed; however, this is still in the nascent phase. Molecular testing by RT-PCR for detection of fusion transcript-positive cells can be employed to detect minimal residual disease in the blood or bone marrow [18].

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