Int J Clin Exp Pathol 2019;12(10):3940-3943
www.ijcep.com /ISSN:1936-2625/IJCEP0100592

Case Report

Ewing's sarcoma/peripheral primitive neuroectodermal tumor with extraskeletal myxoid chondrosarcoma-like areas: a case report

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Received August 5, 2019; Accepted August 28, 2019; Epub October 1, 2019; Published October 15, 2019

Abstract: Introduction: Ewing's sarcoma (EWS)/peripheral primitive neuroectodermal tumor (pPNET) (EWS/pPNET) is a group of highly aggressive small round cell tumors of the bone or soft tissue with high metastatic potential and an aggressive course in children and young adults. EWS/pPNET microscopically does not often have a myxoid background. Case description: We report an EWS/pPNET, which exhibited an unusual morphology with cells having an acidophilic cytoplasm set in a myxoid background, raising the possibility of extraskeletal myxoid chondrosarcoma (EMC). A reverse transcription-polymerase chain reaction analysis confirmed the presence of an EWS-FLI1 fusion transcript. Conclusions: Morphology, immunohistochemistry, and molecular assays may be necessary to avoid a potential diagnostic pitfall as EWS/pPNET with a myxoid background may histologically resemble an EMC.

Keywords: Ewing's sarcoma/peripheral primitive neuroectodermal tumor, extraskeletal myxoid chondrosarcoma, small round blue cells, immunohistochemical, morphology, molecular assays

Introduction

Ewing's sarcoma (EWS) and peripheral primitive neuroectodermal tumor (pPNET) are considered together as a single EWS/pPNET family group because both types share common histopathological, immunophenotype, and genetic abnormalities [1]. In this paper, we describe an uncommon case of EWS/pPNET, which exhibits an unusual morphology with small blue cells and mucous background, raising the possibility of extraskeletal myxoid chondrosarcoma (EMC) because of its complex pathological findings. Histology combined with the immunohistochemical and molecular features are important for diagnosis to clarify their differences.

Case presentation

A 15 year-old boy presented with a chronic onset of non-obvious induced pain in the left femoral area for 20 days. A physical examination revealed a hard, non-mobile mass located at the anterior compartment of the thigh with limitation of movement. Tenderness was evident, and parts of the skin exhibited signs of varicose veins and swelling. A computed tomography scan showed a large low-density soft tissue mass in the upper left femur. Magnetic resonance imaging revealed a mass of 10.4 × 11.3 × 16.4 cm and an abnormal signal with an irregular margin. No change was observed in the bone marrow cavity. A complete surgical excision was performed, and the entire specimen was evaluated. The specimen grossly had a firm mass with a dull-red cut section and a fish-like area. The mass was closely linked to the periosteum and was difficult to distinguish. Striated muscle tissue was observed at the tumor border.

Pathological findings

Microscopy revealed a highly cellular tumor composed of sheets of monotonous round cells with round hyper chromatic nuclei and scant cytoplasms. The tumor cells were mainly composed of small round blue cells with hyperchro-

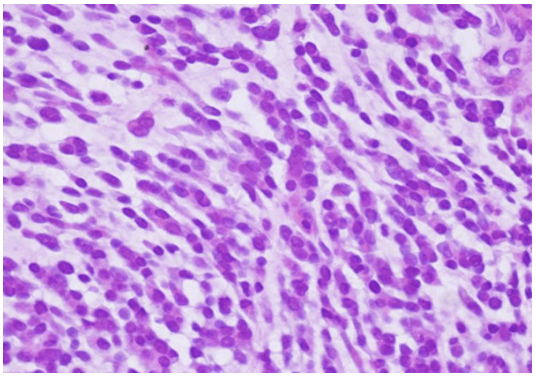

Figure 1. Hematoxylin and eosin (HE) stained section from pathology at × 400 magnification demonstrating the cell morphology.

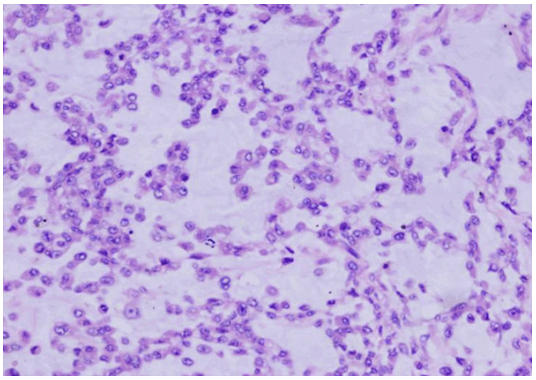

Figure 2. HE stained section of the mucous background at × 200.

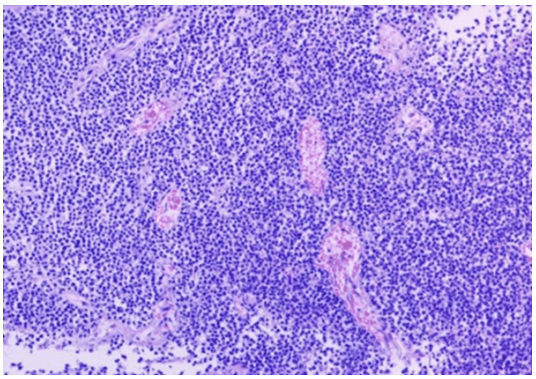

Figure 3. HE stained section of the density of the cells with abundant vessels at × 100.

matic nuclei and minimal red cytoplasms. Some parts of the chromatin were powdery, and some parts of the pink cells deviated in the cytoplasms. Islands of tumors were observed within a fibrous background and presented a small eosinophilic epithelioid malignancy with

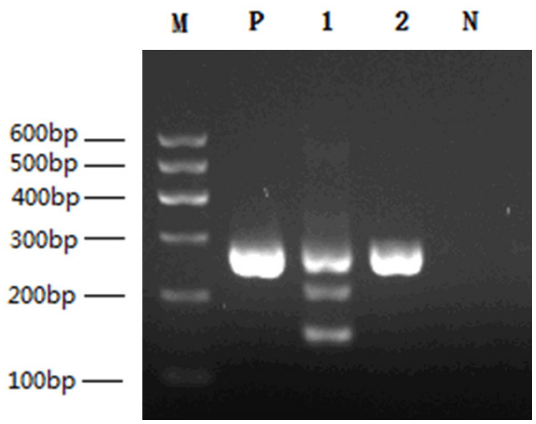

Figure 4. EWS-FLI1 chimeric transcripts were detectable in paraffin-embedded tumors. Lane 1 and lane 2 are separate from the myxoid matrix area and the small round blue cell area obtained by one-step RT-PCR. PCR products of 277 bp correspond to the ES/pPNET fusion gene; M, 600 bp DNA ladder; P, Ewing's sarcoma; N, negative control.

cytoplasmic clearance (**Figure 1**). A few cells were arranged in a mucous background (**Figure 2**). Dense cells with abundant vessels were also found (**Figure 3**). We observed a hemangiopericytoma-like vascular pattern in this neoplasm. Spindle cells were distributed in a braided fibrosarcoma-like pattern, and nuclear fusion and high heteromorphism were also observed. Other features, such as microcapsule structure and necrotic zone, were occasionally formed.

Immunochemistry: vimentin(+), FLI-1(+), WT-1(+), CD56(+), CAM5.2(+), CD138(+), kappa(+), lam-bda(+); NSE(+), CD99(+), CD68(+), LCA(+), CyclinD1(+); MyoD1(-), myogenin(-), EMA(-), AE1/AE3(-), calponin(-), desmin(-), S-100(-), CD34(-), CD79a(-), Bcl-2(-), CD3(-), TdT(-), CD5(-), PAX-5(-), CD21(-).

A one-step reverse transcription-polymerase chain reaction (RT-PCR) was used to detect the fusion gene expression (**Figure 4**). RT-PCR products were obtained from the gel extraction system and connected to a pMD 18-simple T vector for sequencing. The results confirmed the presence of EWS/FLI1.

Discussion

The primitive neuroectodermal tumor (PNET) is a malignant primitive neurogenic small round cell tumor with pluripotent differentiation in an undifferentiated stage. It has two types: the

central primitive neuroepidermal tumor (cPNET) and the peripheral primitive neuroepidermal tumor (pPNET). The most common site of cPNET is the frontal lobe, and the most common site of pPNET is the bones and the soft tissue of the trunk. PNET is a solid mass in the trunk, limbs, and brain parenchyma. pPNET is relatively common, but cPNET is rare, fortunately for both children and adolescents. The age of onset of this case was 15 years old, and the disease was located in the left femur and presented a hard, non-mobile mass, consistent with the pPNET characteristics. The pPNET solid part of the CT showed a slightly higher density, and necrotic cystic changes were observed in the lesion. This feature is consistent with the large amount of necrosis shown under the microscope.

Among the different diagnoses that puzzled us was EMC. EMC mainly occurs in adults. When the proximal mass of the extremities is large, it can cause local pain and discomfort due to peripheral compression. In this case, there was no obvious pain. In EMC, the mucous matrix is abundant and clearly visible, and the tumor cells float in the obvious mucous matrix. In this case, occasionally a slight mucous background in the interstitial is not a characteristic typical realization. In this case, the microscopic examination showed islands of tumor set within a fibrous background. The tumor partly exhibited a small eosinophilic epithelioid malignancy with a cytoplasmic clearance. The tumor was characterized by multilobular structures divided by fibrous septa of varied thicknesses, which is a consistent morphological configuration of EMC. EMC has a multilobular or nodular configuration with a relatively well-defined margin and an incomplete fibrous capsule [2]. Each lobule is typically composed of a proliferation of oval cells arranged in clusters and embedded in an abundant myxoid matrix [3]. The cells sometimes show rhabdoid and epithelioid features and uncommonly present small cell differentiation. The presence of the latter may raise the differential diagnosis of EWS, which may pose a potential diagnostic pitfall as in our case [4].

Immunohistochemistry strongly supported the diagnosis of EWS/pPNET. Immunoreactivity to the CD99 antigen is present in almost all EWS and in peripheral PNET [5]. FLI1 positive is also an important indicator for the diagnosis. The presence of two neuronal markers, synaptophysin and neuronal specific enolase, and the absence of EMA, desmin, smooth muscle actin, cytokeratin, S-100, and LCA should be considered in diagnosing EWS/pPNET [6]. As with all sarcomas, the most diagnostically consistent marker is vimentin [7]. The present case showed strong positive staining for vimentin and other immunohistochemical features, such as cyclinD1, CD138, and kappa, which was similar to previous positive findings.

Molecular assays can often discern EWS/pPNET from other similar tumors. EWS-FLI1, EWS-ERG, EWS-ETV1, EWS-E1AF, and EWS-FEV are different types of translocation fusion genes observed in the EWS/pPNET family of tumors [8]. Of these genes, EWS-FLI1 is important for diagnosis and prognosis. This translocation has been identified in up to 85% to 90% of cases of EWS/pPNET [9]. A minority of tumors will harbor a translocation involving EWSR1 and an alternative partner, the most common of which is ERG located on 21q12 [10]. FLI1 and ERG regulate several genes involved in cellular differentiation and growth. In this case, RT-PCR was used to detect FLI1 and ERG. The FLI1 positive result is consistent with most cases.

Conclusion

In the current case, the histology extremely similar to EMC leaves us perplexed. Immunohistochemistry along with molecular studies are conclusive and definitive for diagnosis. EMC is considered in this case because it has no characteristic immunophenotype and a wide morphological spectrum. A few cases of EMC-like EWS/pPNET have been reported. Our study will serve as a considerable reference in confronting small blue cell tumors.

Acknowledgements

The authors would like to thank our hospital for its help and support for this study. This work was supported by grants from the National Natural Science Foundation of China (Grant no. 81760386).

Disclosure of conflict of interest

None.

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