Case Report of a Subcutaneous Peripheral Primitive Neuroectodermal Tumor

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Abstract. Peripheral primitive neuroectodermal tumors—also known as Ewing sarcomas—are a rare type of malignant tumor the histology of which characteristically reveals the presence of small round cells. Typically, t(11;22) translocation is observed. We describe the case of a 45-year-old man with a subcutaneous peripheral primitive neuroectodermal tumor in which the t(11;22) translocation was detected. He was satisfactorily treated with surgery and radiotherapy.

Key words: peripheral primitive neuroectodermal tumor.
arranged into solid or diffuse, well-vascularized masses or nests with little stroma. Various patterns were observed within the tumor, particularly areas with an alveolar arrangement, lobulated masses, and angiomatoid or pseudoglandular areas. Pseudorosette-like images were seen in some areas (Figure 3). There were few mitoses, and small hemorrhagic foci with hemosiderin deposits were observed. Immunohistochemistry was positive for neuron-specific enolase and negative for chromogranin A, vimentin, synaptophysin, cytokeratins 7 and 20, epithelial membrane antigen, human melanoma antibody-45, S100 protein, CD43HT1, AE1-AE3, and CD45RB-LCA. Staining with CD99 was not performed.

Cytogenetic analysis of the sample performed using fluorescent in situ hybridization (FISH) showed cleavage of the EWS gene resulting from a t(11;22) translocation (Figure 4); together with the previous findings, this confirmed the diagnosis of subcutaneous peripheral primitive neuroectodermal tumor.

Magnetic resonance imaging revealed a well-defined subcutaneous mass situated in the subcutaneous cellular tissue and that was adherent to the fascia of the deltoid muscle, though without infiltration. Computed tomography (CT) did not reveal the presence of metastatic disease, and the lesion was therefore excised with a 2 cm margin, including the muscle fascia. The defect was closed with a full thickness skin graft (Figure 5).

Adjuvant radiation therapy was administered to the tumor bed using a linear electron accelerator (6 MeV), applying a total dose of 66 Gy with 2 Gy/fraction/day, on 5 days each week. In addition, the right axillary lymph node chains were treated with 50 Gy (2 Gy/fraction/day, on 5 days each week) using photons. Subsequently, in the medical oncology department, the patient was also treated with vincristine 2 mg, adriamycin 75 mg/m² and cyclophosphamide 1200 mg/m² for 1 year, with the addition of granulocyte colony stimulating factor every 21 days.

The patient remains disease-free after 25 months of follow-up.

Discussion

Several malignant tumors with histology showing a proliferation of undifferentiated, monomorphic cellular elements with a high nuclear-cytoplasmic ratio are grouped under the term small round cell tumors. Many of these present overlapping clinical-pathologic characteristics and immunohistochemistry, electron microscopy, and cytogenetic analysis are required to reach the correct diagnosis. The low incidence of these tumors and the small number of cases published make it difficult to extrapolate data in an effort to determine the prognosis and most suitable treatment.

The term primitive neuroectodermal tumor refers to a series of tumors showing differentiation towards neuronal tissues. Because of this characteristic, they can affect the central nervous system, parasympathetic ganglia of the autonomic nervous system, and soft tissues, and can also affect peripheral nerves, in which case the term peripheral primitive neuroectodermal tumor (PNET) is used. A large number of authors consider Ewing sarcoma (ES) to be the same as PNET, as they share the t(11;22) translocation. However, other authors distinguish between these tumors as neurosecretory granules are not present in ES and they are therefore considered to be a more primitive form.

The cutaneous form of PNET/ES is even less common, with less than 30 cases published to date. Although it predominates in children and adolescents, the age at presentation is very variable, with a range from 22 months to 81 years. There is no preferential site for these tumors,
as they have been reported on the trunk, limbs, face, and scalp; likewise, no sexual or racial differences have been reported.4

No environmental triggers or familial grouping have been detected.

Clinically, these tumors develop as slow-growing, slightly painful, cutaneous or subcutaneous nodules or masses with a firm or rubbery consistency. Their color is usually similar to that of healthy skin or they can have an erythematous-violaceous hue.4,5

Histologically, PNET/ES can develop in the deep dermis or subcutaneous cellular tissue. It is characterized by dense, solid proliferations of small round cells that, on occasions, are arranged in cords, nests, or lobules. However, the cells have a fusiform appearance in 10% to 20% of cases.6 It is common to find microcystic or pseudovascular spaces that can adopt a reticular pattern. It is also common to find neurophilic material and Homer-Wright rosettes (Table 1). The tumors usually contain fibrovascular septa and foci of necrosis. Individually, the neoplastic cells present minimal, eosinophilic cytoplasm with an oval, hyperchromatic nucleus and disperse chromatin and, in contrast to our case, intense mitotic activity is commonly observed. Rhabdoid and plasmacytoid cells have been identified in some of the cases published.4

Ultrastructurally, round cells with minimal cytoplasm and large, ovoid nuclei are usually observed. These nuclei contain dense heterochromatin and small nucleoli. Microtubules, neuroendocrine granules, and intermediate filaments may be observed in the cytoplasm.7,8

Immunohistochemistry can be positive for vimentin, β2-microglobulin, CD99 (MIC2 membrane antigen), and for other neuronal-markers (S100 protein, Leu-7, neurofilaments, neuron specific enolase, synaptophysin, and protein gene product 9.5); these markers are of great importance for establishing the differential diagnosis with other entities.9

Detection of the t(11;22)(q24;q12) or t(21;22)(q2;q12) translocations using FISH or the reverse transcriptase polymerase chain reaction is considered diagnostic of PNET/ES.10,11 Specifically, the t(11;22)(q24;q12) translocation produces fusion of the EWS gene (located at 22q12) with the Fli1 gene (located at 11q24). Fli1 belongs to a family of transcription factors for a group of proteins called Ets. This fusion produces an aberrant transcription factor that promotes tumorigenesis. Both translocations are detected in 90% to 95% of cases. A third translocation, t(7;22), has been reported recently and has been associated with a poorer prognosis caused by more aggressive disease.12,13

The differential diagnosis mainly involves round cell tumors, and includes Merkel cell carcinoma,14 metastatic small cell lung cancer, metastatic neuroblastoma, cutaneous basaloid adnexal tumors, small-cell malignant melanoma, lymphomas, retiform hemangioendothelioma, angiosarcoma, round cell liposarcoma, and rhabdomyosarcoma. As has been stated above, immunohistochemistry plays a key role in reaching the correct diagnosis (Table 2).15

Due to the small number of cases published, the natural history of PNET/ES is not well defined, although it is thought to have an aggressive behavior in those cases.

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**Table 1. Types of Rosettes and Pseudorosettes**

<table>
<thead>
<tr>
<th>Type</th>
<th>Definition</th>
<th>Subtypes</th>
<th>Tumors in Which They Have Been Described</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosettes</td>
<td>Radial arrangement of tumor cells around neoplastic structures (such as neurofibrillary or other types of material). These are the result of cytoplasmic extensions from the surrounding neoplastic cells</td>
<td>Homer-Wright (with central fibrillary material)</td>
<td>PNET/ES, medulloblastoma, Merkel cell carcinoma, metastatic malignant melanoma, B-cell lymphomas, Ewing sarcoma</td>
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<tr>
<td></td>
<td></td>
<td>Flexner-Wintersteiner (without central neurofibrillary material)</td>
<td>Retinoblastoma</td>
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<td></td>
<td></td>
<td>Others (true ependymal rosette, neurocystic rosettes, pineocytomatous rosettes, etc)</td>
<td>Ependymoma, ependymoblastoma, central neurocytoma, pineocytoma</td>
</tr>
<tr>
<td>Pseudorosettes</td>
<td>Radial arrangement of tumor cells around nonneoplastic structures such as small blood vessels (perivascular pseudorosettes) or other structures (pseudorosettes)</td>
<td>Pseudorosettes</td>
<td>Merkel cell carcinoma, seborrheic keratosis, neuroblastoma-like neurilemmoma (rosetoid schwannoma), cutaneous melanocytoneuroma, Spitz nevus, dendritic cell neurofibroma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Perivascular pseudorosettes</td>
<td>Ependymomas, glioblastomas, PNET/ES, meningioma, astroblastoma, etc</td>
</tr>
</tbody>
</table>

Abbreviations: ES, Ewing sarcoma; PNET, peripheral primitive neuroectodermal tumor.
developing in deeper regions, in large tumors, and in those with the t(7;22) translocation.12

Taylor8 published a series of 31 patients with PNET/ES. Four of those patients died of metastatic disease, 5 developed locoregional lymph node metastases, and the other cases remained disease-free after 42 months. There appears to be no correlation between the clinical-histopathologic type and the metastatic potential, though the type does correlate with the presence of intense necrosis and vascular invasion.

In view of the above, we do not know the best treatment for this tumor, though it is generally accepted that the combination of surgery, radiation therapy, and chemotherapy achieves a significant increase in survival and in the disease-free interval.

Conclusion

We present a case of subcutaneous PNET/ES with typical cytogenetic findings. The disease responded satisfactorily to combined treatment with surgery, radiation therapy, and chemotherapy. The broad differential diagnosis associated with this tumor makes histologic, immunohistochemical, and cytogenetic analysis essential to reach the correct diagnosis.

Conflicts of Interest

The authors declare no conflicts of interest.

Table 2. Immunohistochemical Differential Diagnosis of Tumors With Round Cells on Histologic Study

<table>
<thead>
<tr>
<th></th>
<th>CK</th>
<th>Vim</th>
<th>S100</th>
<th>EMA</th>
<th>b2m</th>
<th>CD99</th>
<th>NSE</th>
<th>CD31</th>
<th>CLA</th>
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<tbody>
<tr>
<td>PNET/ES</td>
<td>+/-</td>
<td>+</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
<td>+/-</td>
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<tr>
<td>Merkel cell carcinoma</td>
<td>+</td>
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<td>+</td>
<td>-</td>
<td>+/-</td>
<td>+</td>
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<tr>
<td>Metastasis of small cell lung cancer</td>
<td>+</td>
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<td>+/-</td>
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<tr>
<td>Metastatic neuroblastoma</td>
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<td>Basaloid adnexal tumors</td>
<td>+/-</td>
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<td>Glomic cell tumor</td>
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<tr>
<td>Small-cell malignant melanoma</td>
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<td>+</td>
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<td>Lymphomas</td>
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<tr>
<td>Retiform hemangiendothelioma</td>
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<td>+/-</td>
<td>+/-</td>
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<td>Angiosarcoma</td>
<td>+/-</td>
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<td>+</td>
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<td>Round cell liposarcoma</td>
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<td>+</td>
<td>+/–</td>
<td>+/-</td>
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<tr>
<td>Rhabdomyosarcoma</td>
<td>+/-</td>
<td>+</td>
<td>+/-</td>
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<td>+/-</td>
<td>+/-</td>
<td>+/–</td>
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</tbody>
</table>

Abbreviations: b2m, β2-microglobulin; CLA, common leukocyte antigen; CK, cytokeratin; Des, desmin; EMA, epithelial membrane antigen; NSE, neuron-specific enolase; Vim, vimentin; +, positive in > 90% of cases; +/-, occasionally positive; –/+, positive in isolated cases; –, negative.

References


