

CASE REPORTS

Case Report of a Subcutaneous Peripheral Primitive Neuroectodermal Tumor

R. Cabrera, P. Sánchez, and M.A. Rodríguez

Servicio de Dermatología, Complejo Asistencial de León, León, Spain

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.

TUMOR SUBCUTÁNEO NEUROECTODÉRMICO PRIMITIVO PERIFÉRICO. A PROPÓSITO DE UN CASO

Resumen. La familia del tumor neuroectodérmico primitivo periférico/sarcoma de Ewing (PNET/ES) representa a un grupo de neoplasias malignas poco frecuentes, incluidas dentro de un grupo de tumores que presentan característicamente en su histología células redondas de pequeño tamaño. La traslocación 11;22 es típica de este tumor. Se presenta el caso de un varón de 45 años con un tumor subcutáneo neuroectodérmico primitivo periférico, en el que se detectó la traslocación t(11;22), tratado satisfactoriamente mediante cirugía y radioterapia.

Palabras clave: tumor neuroectodérmico primitivo periférico.

Case Report

A 45-year-old man, with no past history or family history of interest, was seen for an asymptomatic lesion on the right shoulder that had appeared 5 months earlier and had grown progressively. The patient denied weight loss, asthenia, fever, or general malaise during this period.

On physical examination, a firm, erythematous-violaceous, subcutaneous tumor lesion of 6 × 7 cm was observed, adherent to the deep planes. The surface presented scabs and telangiectasias (Figure 1), and there were no palpable locoregional lymph nodes. There were no significant abnormalities in the complete blood count or routine biochemistry tests. Ultrasound study revealed a lesion of 3.8 × 4.3 × 3.8 cm with well-defined, smooth borders and

a heterogeneous content formed of hyperechogenic lobules, blood vessels, and fluid-filled cystic areas. A chocolate-colored material was obtained on fine-needle aspiration and was sent for pathologic study, being reported as a population of uniform cells with little cytoplasm, nuclei with irregular chromatin, and an absent or inconspicuous nucleolus, suggestive of a malignant round cell tumor, possibly of neuroectodermal origin.

Histopathologic examination of the biopsy revealed a neoplastic proliferation of medium-sized round cells located in the hypodermis, extending towards the deep dermis and with no epidermal involvement. The cells presented a round or oval nucleus with finely granular chromatin, an inconspicuous nucleolus, and minimal cytoplasm (Figure 2), together with intracytoplasmic vacuoles. The cells were

Correspondence:
Roberto Cabrera Paz
Camino de Triana, 8
38760 Los Llanos de Aridane
Isla de La Palma
Santa Cruz de Tenerife, Spain
rcp1312@yahoo.es

Manuscript accepted for publication March 5, 2008.



Figure 1. Erythematous tumor lesion of 6 × 7 cm, with scabs on the surface.

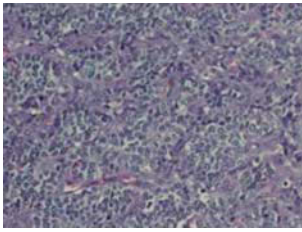


Figure 2. Proliferation of round cells with hyperchromatic nuclei (hematoxylin-eosin ×400).

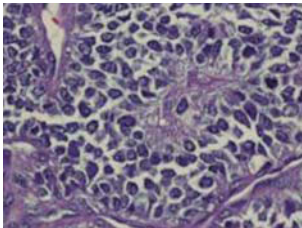


Figure 3. Pseudorosettes with eosinophilic fibrillary material surrounded by tumor cells arranged in circles (hematoxylin-eosin ×400).

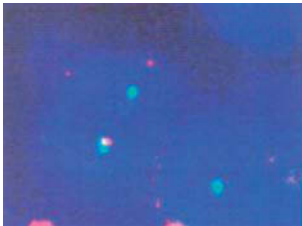


Figure 4. t(11;22) translocation detected by fluorescent in situ hybridization.



Figure 5. Excision of the lesion including the muscle fascia.

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.¹ 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.² 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.³

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,

Table 1. Types of Rosettes and Pseudorosettes

Type	Definition	Subtypes	Tumors in Which They Have Been Described
Rosettes	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	Homer-Wright (with central fibrillary material)	PNET/ES, medulloblastoma, Merkel cell carcinoma, metastatic malignant melanoma, B-cell lymphomas, Ewing sarcoma
		Flexner-Wintersteiner (without central neurofibrillary material)	Retinoblastoma
		Others (true ependymal rosette, neurocytic rosettes, pineocytomatous rosettes, etc)	Ependymoma, ependymblastoma, central neurocytoma, pineocytoma
Pseudorosettes	Radial arrangement of tumor cells around nonneoplastic structures such as small blood vessels (perivascular pseudorosettes) or other structures (pseudorosettes)	Pseudorosettes	Merkel cell carcinoma, seborrhic keratosis, neuroblastoma-like neurilemmoma (rosetoid schwannoma), cutaneous melanocytoneuroma, Spitz nevus, dendritic cell neurofibroma
		Perivascular pseudorosettes	Ependymomas, glioblastomas, PNET/ES, meningioma, astroblastoma, etc

Abbreviations: ES, Ewing sarcoma; PNET, peripheral primitive neuroectodermal tumor.

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, β 2-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

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

	CK	Vim	S100	Des	EMA	b2m	CD99	NSE	CD31	CLA
PNET/ES	-/+	+	+/-	-/+	-	+	+	+/-	-	-
Merkel cell carcinoma	+	-	-	-	+	-	-/+	+	-	-
Metastasis of small cell lung cancer	+	-	-	-	-	-/+	-/+	-	-	-
Metastatic neuroblastoma	-	-	+	-	-	-	-	+	-	-
Basaloid adnexal tumors	+/-	+/-	+/-	+	+	-	-	-/+	-	-
Glomic cell tumor	-	+	-	+/-	-	-	-	-	+	-
Small-cell malignant melanoma	-	+	+	-	-	-	-	+	-	-
Lymphomas	-	+/-	-	-	-/+	+/-	+/-	-	-	+/-
Retiform hemangioendothelioma	-	+/-	-	-	-	-	-/+	-	+	-
Angiosarcoma	-/+	+	-	-	-	-	-	-	+	-
Round cell liposarcoma	-	+	-	+/-	-	-	-	-	-	-
Rhabdomyosarcoma	-/+	+	-/+	+	-	-	+/-	+/-	-	-

Abbreviations: β 2m, β 2-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.

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.

References

1. Devoe K, Weidner N. Immunohistochemistry of small round-cell tumors. *Semin Diagn Pathol.* 2000;17:216-24.
2. Sanguenza OP, Sanguenza P, Valda LR, Meshul CK, Requena L. Multiple primitive neuroectodermal tumors. *J Am Acad Dermatol.* 1994;31:356-61.
3. Whang-Peng J, Triche TJ, Knusten TJ. Cytogenetic characterization of selected small round cell tumors of childhood. *Cancer Genet Cytogenet.* 1986;21:185-208.
4. Banarjee SS, Agbamu DA, Eyd BP. Clinicopathological characteristics of peripheral primitive neuroectodermal tumour of skin and subcutaneous tissue. *Histopathology.* 1997;31:355-66.
5. Jacinto CM, Grant-Kels JM, Knibbs DR. Malignant primitive neuroectodermal tumor presenting as a scalp nodule. *Am J Dermatopathol.* 1991;13:63-70.
6. Lodding P, Kindblom LG, Angervall L. Epithelioid malignant schwannoma, a study of 14 cases. *Virchows Arch.* 1986;409:433-51.
7. Pappo AS, Cheah MS, Saldivar VA. Disseminated primitive neuroectodermal tumor: diagnosis using immunocytochemistry, electron microscopy and molecular probes. *Cancer.* 1989;63:2515-21.
8. Taylor GB, Chan YF. Subcutaneous primitive neuroectodermal tumour in the abdominal wall of a child: long-term survival after local excision. *Pathology.* 2000;32:294-8.
9. Lee CS, Southey MC, Slater H. Primary cutaneous Ewing's sarcoma/peripheral primitive neuroectodermal tumors in childhood. A molecular, cytogenetic and immunohistochemical study. *Diagn Mol Pathol.* 1995;4:174-81.

10. Yamaguchi U, Hasegawa T, Morimoto Y. A practical approach to the clinical diagnosis of Ewing's sarcoma/primitive neuroectodermal tumour and other small round cell tumours sharing EWS rearrangement using new fluorescence in situ hybridisation probes for EWSR1 on formalin fixed, paraffin embedded tissue. *J Clin Pathol.* 2005;58:1051-6.
11. Hua W, Jie Z, Yu-ping W. Molecular detection of EWS-Ets fusion transcripts and their clinicopathologic significance in Ewing's sarcoma/peripheral primitive neuroectodermal tumor. *Chin Med J.* 2005;118:1323-9.
12. Smith ML, Roberta H. Peripheral primitive neuroectodermal tumor presenting with diffuse cutaneous involvement and 7;22 translocation. *Med Pediatr Oncol.* 1998;30: 357-63.
13. Somers GR, Shago M, Zielenska M, Helen SL, Ngan BY. Primary subcutaneous primitive neuroectodermal tumor with aggressive behavior and an unusual karyotype: case report. *Pediatr Dev Pathol.* 2004;7:538-45.
14. Ruiz R, Blasco J, Merino J, Linares J, Naranjo R. Carcinoma de células de Merkel. Presentación de seis casos. *Actas Dermosifiliogr.* 2003;94:300-4.
15. Nicholson SA, McDermott MB, Swanson PE, Wick MR. CD 99 and cytokeratin-20 in small-cell and basaloid tumors of the skin. *Appl Immunohistochem Mol Morphol.* 2000;8: 37-41.