



Case Report

Pulmonary Ewing Sarcoma/Primitive Neuroectodermal Tumor: A Case Report and a Review of the Literature

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ARTICLE INFO

Article history:

Received March 24, 2009

Accepted April 2, 2009

Available online August 4, 2009

Keywords:

Ewing sarcoma/primitive neuroectodermal tumor

Primary lung tumor

Diagnosis

Palabras clave:

Sarcoma de Ewing/PNET

Tumor pulmonar primario

Diagnóstico

ABSTRACT

Primary thoracic sarcomas are very rare. The most common intrathoracic variants are synovial sarcoma, angiosarcoma, leiomyosarcoma, rhabdomyosarcoma, and sarcomatoid mesothelioma. Although thoracic Ewing sarcoma/primitive neuroectodermal tumor (PNET) usually develops on the chest wall, there have been reports of primary Ewing sarcoma/PNET of the lung.

We present the case of a 22-year-old woman with Ewing sarcoma/PNET diagnosed following histologic, immunohistochemical, and in situ hybridization studies of a bronchial biopsy specimen. Radiography, ventilation-perfusion scintigraphy, and a bone marrow biopsy confirmed that the tumor was not metastatic. The patient was started on a chemotherapy regimen of vincristine, actinomycin, cyclophosphamide, doxorubicin, ifosfamide, and etoposide and responded well. She is now being seen regularly at our outpatient clinic.

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Sarcoma de Ewing pulmonar/tumor neuroectodérmico primitivo (PNET): aportación de un caso y revisión de la bibliografía

RESUMEN

Los sarcomas primarios de tórax son muy poco frecuentes. Sarcoma sinovial, angiosarcomas, leiomiomas, rhabdomyosarcomas y mesoteliomas sarcomatoides son las variantes intratorácicas más comunes. Aunque el sarcoma de Ewing/tumor neuroectodérmico primitivo (PNET) torácico se desarrolla habitualmente en la pared torácica, se ha descrito en la literatura médica algún caso de localización pulmonar primaria.

Presentamos el caso de una mujer de 22 años diagnosticada de sarcoma de Ewing/PNET pulmonar mediante muestra bronoscópica por sus características histológicas, inmunohistoquímicas y técnicas de hibridación in situ. Se excluyó el origen metastásico mediante radiografía, gammagrafía y biopsia de médula ósea. Se inició quimioterapia según el esquema VACD-IE (vincristina, actinomicina D, ciclofosfamida, doxorubicina, ifosfamida y etopósido), con buena respuesta. En la actualidad acude de forma regular a consultas ambulatorias.

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Introduction

Ewing sarcoma of the bone is the second most common type of primary bone cancer, exceeded only by osteosarcoma.^{1,2} At the time of diagnosis, 24% of patients have metastatic disease, which most commonly affects the lungs, followed by other bones and bone

marrow. It is a member of the Ewing family of tumors, together with primitive neuroectodermal tumor (PNET), Askin tumor (Ewing sarcoma affecting the chest wall), and extraosseous Ewing sarcoma. These tumors are grouped together because they have almost identical pathologic, immunohistochemical, and genetic features. Ewing sarcoma forms mainly in the long bones of the axial skeleton and most often affects the diaphyses. The mean age of onset is 15 years and it is slightly more common in males. When located in the thorax, it mostly affects the ribs (Askin tumor). While lungs may be affected by metastases, primary lung involvement is extremely rare and has a slightly later age of onset (around 20 years).

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Histologically, it is characterized by a sheet of small round blue cells that react positively to glycoprotein p30/32 MIC2 (CD99). Rearrangement of the *EWS* gene, which, in conjunction with the above histologic findings, is pathognomonic, is seen in a high proportion of cases.

The most common clinical manifestations are bone pain and swelling and general symptoms such as malaise and fever, with fever being more common in patients with metastatic disease. Diagnosis cannot be made on the basis of clinical, laboratory, or imaging findings, hence the need for a biopsy and immunohistochemical and molecular biology studies. Seventy-five percent of patients have localized disease. The overall survival in such cases is approximately 70%, a figure that drops to 26% when there is metastasis. Treatment consists of surgery (when the tumors are operable and resectable) and adjuvant chemotherapy.

Case Description

We describe the case of a 22-year-old nonsmoking woman with no relevant history who presented at the emergency department with fever that had started a week earlier and generalized muscle pain. The physical examination was unremarkable except for low-grade fever (37.6 °C). A chest radiograph revealed an opaque mass measuring approximately 5 cm in the right hemothorax and partial



Figure 1. Radio-opaque mass in middle lobe and lower right lobe.



Figure 2. Right parahilar mass with distal pneumonitis.

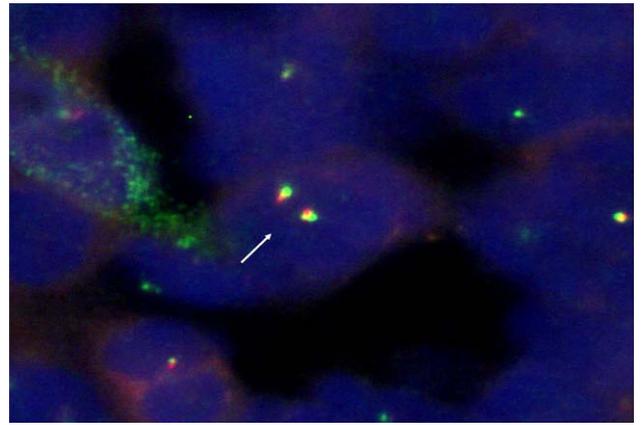


Figure 3. Infiltration by Ewing sarcoma. Splitting signals can be seen in *EWS* (translocation of gene).

atelectasis of the middle lobe and right lower lobe (Figure 1), and it was decided to admit the patient for further evaluation. The laboratory tests, which included assessment of thyroid hormones and tumor markers, were completely normal. A computed tomography (CT) scan of the thorax, abdomen, and pelvis showed a mass measuring 5 cm × 4 cm in the right parahilar region, with distal obstructive pneumonitis (Figure 2). There were no other remarkable CT findings. During the fiberoptic bronchoscopy, we observed infiltration of the mucosa of the right intermediate bronchus, with partial stenosis of the middle and right lower lobes.

Examination of the bronchial biopsy specimen showed small round tumor cells with scant cytoplasm. The results of the immunohistochemical study were as follows: CD99, positive; synaptophysin, positive; neuron-specific enolase (NSE), negative; S-100, negative; CD56, negative; thyroid transcription factor-1 (TTF-1), negative; chromogranin, negative; cytokeratin AE1-AE3, negative; cytokeratin 7, negative; cytokeratin 18, negative; and lymphoid markers (LC, CD20, and CD3), negative. The fluorescent in situ hybridization (FISH) study of the *EWS* gene (Figure 3) showed gene rearrangement (splitting signals from majority of nuclei), indicating translocation of the gene. All these findings provided unequivocal evidence of Ewing sarcoma/PNET.

A definitive diagnosis of primary Ewing sarcoma/PNET of the lung was made following a negative staging evaluation, consisting of a cranial CT, bone scintigraphy, a bone marrow biopsy, and analysis of the CT chest scan. The patient was transferred to the oncology department, where she was started on a chemotherapy regimen³⁻⁵ of vincristine, actinomycin, cyclophosphamide, doxorubicin, ifosfamide, and etoposide,⁶ with good initial response.

Discussion

Ewing sarcoma is the second most common primary bone cancer, exceeded only by osteosarcoma.^{1,2} It generally presents in patients in their 20s, although 20% to 30% of cases are diagnosed at a younger age. Primary extraosseous tumors are rare, with the most common sites being the chest wall, the paravertebral muscles, the buttocks, and the retroperitoneal space. There have, however, been anecdotal reports of other sites⁷ including the kidney, the breast, the gastrointestinal tract, the prostate, the endometrium, the jaw, the adrenal glands, and the meninges. In a review of the literature using MEDLINE and PubMed (1978-2008) and the search terms *Ewing's sarcoma* and/or *primitive neuroectodermal tumor*, we found just 9 reports of primary lung involvement,⁸⁻¹¹ only 2 of which^{12,13} included a genetic study. It is surprising that almost all of the studies had been

published by Japanese groups, with no reports from Europe or North America.

Our patient had no symptomatic evidence of lung disease, just nonspecific symptoms consisting of low-grade fever and muscle pain. This is consistent with reports from the majority of cases published. The radiologic images did not reveal any specific abnormalities and simply served to confirm that the tumor had not originated on the chest wall or metastasized from another location. (The lung is the site for metastasis in 10% of cases). The gross bronchoscopic findings were also unremarkable and failed to reveal any features that distinguished the mass from other lung tumors. Nonetheless, this is the second report of an endobronchial lesion in such cases and in which diagnosis was confirmed using a bronchial biopsy specimen. The age of the patient and the small round cells seen in the histopathologic analysis provided important clues about the type of tumor involved and prompted the use of other confirmation methods.

Histologically, Ewing sarcoma is characterized by a sheet of small blue round cells that react positively to glycoprotein p30/32 MIC2 (CD99) with monoclonal antibodies including O13, 12E7, and HBA71. Ewing tumor cells also show immunoreactivity to vimentin and synaptophysin. PNET, which is the most differentiated of the Ewing sarcoma family tumors, may also test positive to differentiated neuronal markers such as NSE, S-100, Leu-7, and PgP9.5, and 20% percent of PNETs show positivity to cytokeratins. Even though Ewing sarcoma has specific histologic and phenotypic features, differential diagnosis should include other small round cell pediatric tumors such as neuroblastoma, lymphoblastic lymphoma, and rhabdomyosarcoma as treatment approaches differ. Like Ewing sarcoma, neuroblastoma shows immunoreactivity to NSE, S-100, and Leu-7, but it also tests positive for neurofilament proteins and negative for vimentin. Lymphoblastic lymphoma is similar to Ewing sarcoma in that it is immunoreactive to CD99 but different in that it tests positive to lymphoid markers, leukocyte common antigen (CD45), and terminal deoxynucleotidyl transferase. Rhabdomyosarcoma differs from Ewing sarcoma in that it is immunoreactive to myogenin, myo-D1, desmin, and actin. It is sometimes difficult to distinguish poorly differentiated synovial sarcoma from Ewing sarcoma as both show positive results for CD99 and cytokeratins. In our patient, the immunohistochemical study showed positive reactions to CD99 and synaptophysin and negative reactions to S-100, CD56, CD45, TTF-1, chromogranin, cytokeratins (AE1/AE3, 7, 18), lymphoid markers (LC, CD20, and CD3) and desmin. Molecular genetic studies using FISH or reverse transcription and polymerase chain reaction can be used to confirm diagnosis in cases with equivocal immunohistochemical results. The

translocation t(11,22)(q24;q12) is pathognomonic of Ewing sarcoma. It occurs in 85% of patients and gives rise to the formation of the *EWS-Flil* gene. The remaining 15% of patients have variants of this translocation, including 22q12, 21q2 (10% of cases) and 7p22, 17q12, 2q36 (<1% of cases). Structural changes other than translocations may also occur. Examples include trisomy 8 or 12, deletions of 9p21, and loss of heterozygosity of 17p13. In our patient, FISH of the *EWS* gene showed rearrangement (splitting signals from practically all of the nuclei), indicating that the gene had been translocated. This rearrangement is seen in other tumors such as desmoplastic small round cell tumor sarcoma and soft tissue melanomas, but these have different histologic features. To reach a diagnosis, it is therefore essential to take account of numerous factors, including suspicious signs and symptoms and histopathologic, immunohistochemical, and genetic findings.

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