Primitive Neuroectodermal Tumor of the Lung

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Primitive neuroectodermal tumors (PNETs) occur most frequently in the bone and soft tissues of children or young adults. The most common sites of origin for osseous lesions are the long bones, such as the femur or humerus or the pelvic bones. Soft tissue lesions arise more frequently in the deep tissues of the paravertebral or thoracic regions, lower extremities, and pelvis.

Infrequently, PNETs have been described in other organs, such as the kidney, as primary neoplasms, or as arising from other tumors, such as ovarian or testicular germ cell neoplasms.1-5 Those PNETs that arise in the lung parenchyma without pleural or chest wall involvement are extremely rare, and to our knowledge only 5 cases have been reported, 3 of them with follow-up.6-8

We report an additional case of a PNET of pulmonary origin with a full clinical follow-up and ancillary pathological techniques used in diagnosis.

REPORT OF A CASE

An 18-year-old man was admitted because of deterioration of health, dyspnea, cough, and hemoptysis. Chest radiograph and computed tomographic scan showed a mass in the right middle lobe, and bronchoscopy revealed an endobronchial tumor. Surgery was performed, removing the lesion by a middle lobectomy. No adjunct radiation or chemotherapy was given.

After a 2-year disease-free period, a local recurrence was found on a chest radiograph. No evidence of metastatic disease was found clinically. At surgery, the tumor extensively involved the lung with invasion of the pulmonary veins and right atrium. Right upper and lower lobectomy was performed, with partial resection of the right atrium. The patient died 2 days after surgery.

PATHOLOGIC FINDINGS

Initial Surgery

The right middle lobectomy specimen weighed 85 g. The cut surface revealed a brownish, solid, circumscribed tumor that measured $4 \times 3 \times 3$ cm and extensively involved the bronchial lumen. The surgical margin was free of tumor, and the pleura and lymph nodes were not involved.

On light microscopic examination, the neoplasm was composed of sheets and cords of small cells with uniform appearance, scanty or indistinct cytoplasm, and round-to-oval nuclei, with coarse but evenly distributed chromatin. Nucleoli were rarely visible. Mitotic activity was moderate. Rosettes were observed with cells surrounding a central core of fibrillary material (Homer-Wright rosettes) (Figure 1). Necrosis of the tumor was extensive, and vein and lymphatic invasion was observed.

A periodic acid–Schiff stain was focally positive, and the positivity was abolished by diastase digestion.

Immunohistochemical stains were performed on sections from the paraffin-embedded blocks. Antigen retrieval was enhanced by the use of a microwave oven and citrate buffer. The following monoclonal antibodies and dilutions were used: cytokeratin (AE1-AE3, Boehringer, Indianapolis, Ind, 1:200), chromogranin (Dako Corporation, Carpinteria, Calif, 1:80), synaptophysin (Dako, 1:50), neuron-specific enolase (NSE; Dako, 1:400), neurofilaments (Dako, 1:100), CD99 (O13, Signet, St Louis, Mo, 1:150), vimentin (Dako, 1:60), and CD45 (Dako, 1:50). The avidin-biotin method (Vectastain Elite, Vector Laboratories, Burlingame, Calif) was used as detection system, diaminobenzidine as a chromogen, and hematoxylin as a counterstain. Appropriate positive and negative controls were used. The tumor showed a strong and diffuse positivity with vimentin and CD99 and focal immunostaining with NSE and neurofilaments (Figure 2). The other markers were negative.

For ultrastructural studies, formalin-fixed tumor samples were washed, postfixed in buffered osmium tetroxide, dehydrated, and embedded in epoxy resin. Ultrathin sec-
Figure 1. Photomicrograph of the tumor showing small cells with scanty cytoplasm and rosette formation (hematoxylin-eosin, original magnification ×400).

Figure 2. Strong staining of the tumor with O13 (O13, original magnification ×400).

Figure 3. Electron microphotograph showing few dense core neurosecretory granules (original magnification ×4400) (arrows), which are shown in more detail in the insert (original magnification ×12,000).

COMMENT

Our case showed the histological, histochemical, immunohistochemical, and ultrastructural features of PNETs. This diagnosis, once difficult for the surgical pathologist, is greatly facilitated now by the availability of antibodies such as HBA-71, 12E7, and O13 that recognize the cell surface antigen defined by the cluster of CD99. Although not specific for PNET or Ewing sarcoma, CD99 is almost always present in these tumors. It must be used together with antibodies to vimentin, NSE, neurofilaments, and other markers determined by the differential diagnosis of the individual case to exclude lymphoma, carcinoma, or sarcoma.

In lung tumors, the immunohistochemical differential diagnosis is complicated, since CD99 can be found in small cell carcinomas and up to 30% of carcinoid tumors. Occasionally, PNETs stain with chromogranin and synaptophysin, and aberrant expression of cytokeratin has also been reported. Small cell carcinomas and carcinoid tumors are almost always cytokeratin positive. Thus, a phenotype such as found in our case, which was CD99, vimentin, NSE, and neurofilament positive and cytokeratin, synaptophysin, and chromogranin negative, is highly suggestive of PNET.

Electron microscopy can be used to confirm immunohistochemical results, indicating a tumor to be a PNET. Ultrastructural analysis usually shows PNET cells to have complex cytoplasmic processes, microtubules, and few neurosecretory granules, such as we found in our case. In contrast, the cells of small cell carcinoma have few organelles and an irregular heterochromatin pattern. Carcinoid tumor cells contain numerous dense core granules, which vary considerably in shape and size.

Cytogenetic studies have demonstrated a characteristic reciprocal translocation t(11;22)(q24;q12) that seems specific for PNETs and Ewing sarcoma.

Those PNETs that arise in uncommon sites are well described in the literature. Almost all are case reports of tumors located in the kidney, urinary bladder, myocardium, pancreas, retroperitoneum, and the female genital tract.
There are only 5 cases of PNETs reported as arising as primary tumors in the lung without pleural or chest wall involvement. These criteria can be used to differentiate PNETs that arise in the lung from the more common Askin tumors. In Askin's original series, there were no instances of isolated nonpleural-based parenchymal disease among their 20 cases.

The patients with pulmonary PNET previously described had an age range of 15 to 64 years, with a mean age of 33 years. They were treated with various combinations of surgery, chemotherapy, and radiation therapy. Of the 3 patients with follow-up, one, treated with surgery and chemotherapy, is alive without disease at 2 years after surgery, another is alive with distant metastasis at an unstated period, and the other, treated with surgery, is dead of widespread metastatic disease 2 years after operation.

Based on this small number of cases, pulmonary PNETs are aggressive neoplasms that have a clinical course similar to PNETs of other organs. In general, almost all patients who developed metastases die of their disease as do 75% of patients with localized disease. The treatment of choice is early surgical removal with intensive chemotherapy and radiation therapy to ablate residual microscopic disease.

This study was supported by the Center of Medical Education and Clinical Investigations.

References