

Primary pulmonary extraskelatal Ewing sarcoma/Primitive neuroectodermal tumor: Two case reports

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Primary pulmonary extraskelatal Ewing sarcoma (EES)/primitive neuroectodermal tumor is an extremely rare tumor with only few cases reported in the literature. In this study, we present two cases of primary pulmonary EES diagnosed and treated at our institution. The median age was 20 years (range: 19–21). Cough, dyspnea, and hemoptysis were the predominant features at presentation, associated with a large lung mass on imaging. Image-guided core needle biopsies were the diagnostic modalities for both patients. Initial histopathology showed malignant small round cell tumor, which has been confirmed by immunohistochemistry as EES. Both patients received neoadjuvant chemotherapy followed by surgery; postoperative pathology for the first patient showed 98% tumor necrosis, whereas the second patient's pathology showed no evidence of residual tumor after complete surgical excision.

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Introduction

Ewing's sarcoma family is a group of aggressive tumors, mostly arising from bone. It was first described in 1921 by American pathologist James Ewing [1]. This group of tumors includes Ewing sarcoma (osseous and extraosseous), primitive neuroectodermal tumor (PNET) of the bone and soft tissues, Askin tumor (PNET of the thoracopulmonary region), and other less common tumors (e.g. ectomesenchymoma and peripheral medulloepithelioma) [2]. Ewing sarcoma usually presents during the second decade of life with male predominance [3]. Extraskelatal Ewing's sarcoma of the lung is exceedingly rare, with only few cases reported [2]. We present in this study two cases of primary extraskelatal Ewing's sarcoma of the lung diagnosed and treated at our institution (Al-Azhar University Hospitals, Cairo, Egypt), to highlight the importance of clinical, radiological, and pathological integration in the evaluation of such cases.

Case report 1

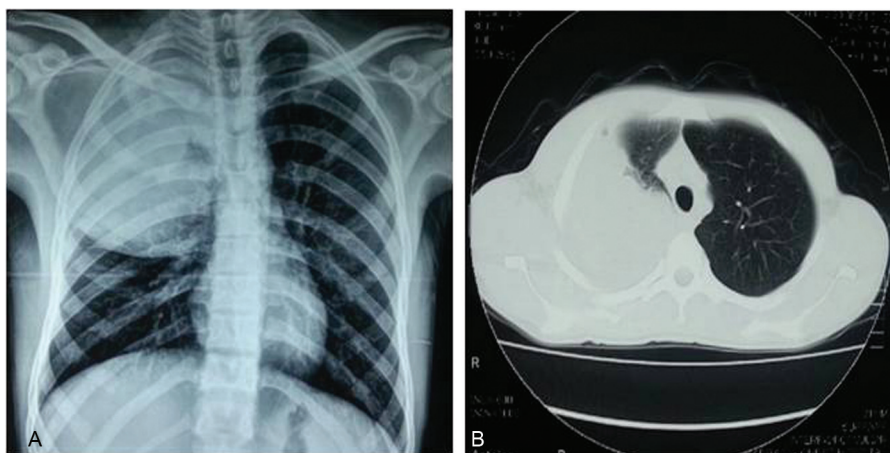
A 21-year-old male patient presented with right-sided chest pain, cough with hemoptysis of blood-tinged sputum, fever, malaise, and loss of weight of 2 months' duration. The patient received several courses of antibiotics for presumed pneumonia and NSAIDs before presentation to our hospital without improvement.

At presentation, the patient was feverish and had signs consistent with lung mass on examination. Plain chest radiography showed large homogeneous opacity in the

right lung involving the upper and middle lung zones (Fig. 1a). Computed tomography (CT) of the chest with intravenous contrast showed a large heterogeneous mass in the right upper lobe measuring about 9×10 cm (Fig. 1b). Thoracic ultrasound showed a large hypoechoic lesion in the right upper anterior chest measuring about 8×11 cm with irregular margins, with anechoic areas of breakdown and static air bronchogram. Fiberoptic bronchoscopy was performed and showed narrowing of all segmental bronchi of the right upper lobe, broadening of the carina and congested fragile mucosa. Transthoracic ultrasound-guided tru cut needle biopsy was performed and revealed markedly cellular tumor composed of malignant round cells with relatively monomorphic round nuclei. Some nuclei showed stippled chromatin, and others were hyperchromatic. The cytoplasm ranged from abundant clear to scanty eosinophilic. Sheets of tumor tissue showed focal apoptosis and necrosis with intervening fibrocollagenous stroma (Fig. 2a). Immunostaining of the sections prepared from the blocks using CD99 antibody revealed strong continuous cell membrane staining. Tumor cells showed negative staining for leukocyte common antigen (LCA), thyroid transcription factor 1 (TTF1), and pancytokeratin (AE1/AE3) (Fig. 2b); these findings were compatible with extraskelatal Ewing's

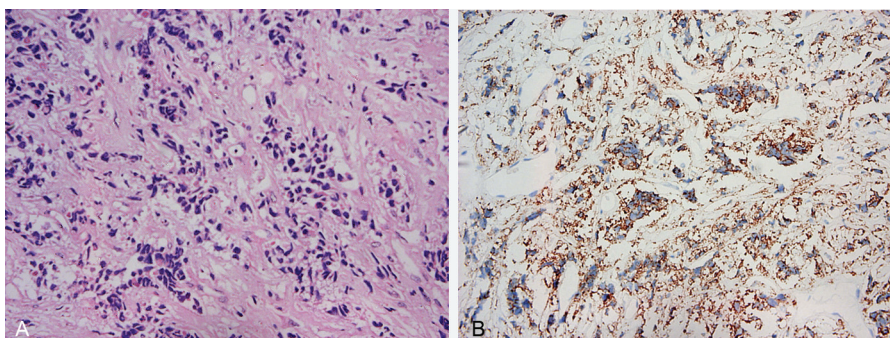
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Figure 1



A: Plain chest x-ray shows large homogeneous opacity in right lung involving upper and middle lung zones. B: CT chest shows a large heterogeneous mass in right upper lobe about 9×10 cm

Figure 2



A: Histopathology slide shows markedly cellular tumor composed of malignant round cells with relatively monomorphic round nuclei. The cytoplasm ranged from abundant clear to scanty eosinophilic. Sheets of tumor tissue showed focal apoptosis and necrosis with intervening fibrocollagenous stroma (H&E). B: Immunostaining using CD99 antibody shows strong continuous cell membrane staining.

sarcoma. Patient was treated with neoadjuvant chemotherapy [alternating VAC (vincristine 1.5 mg/m² day 1, adriamycin 25 mg/m² days 1–3, and cyclophosphamide 1200 mg/m² day 1 with mesna) and IE (ifosfamide 1800 mg/m² days 1–5, with mesna and etoposide 100 mg/m² days 1–5). He finished six cycles of chemotherapy with good partial response, and then was assessed for surgical resection that was borderline at this time, and so the patient received another two cycles of carboplatin AUC5 (total duration of chemotherapy 23 weeks). Subsequently, the patient underwent right upper lobectomy. The postoperative pathology showed 98% tumor necrosis. The patient recovered well from surgery and he is still under regular follow-up and free of disease until now (16.1 months).

Case report 2

A 19-year-old female patient presented to us with complains of progressive cough, dyspnea, and chest wall pain for 8 months' duration with chest tube inserted on the right side. The patient was managed

as a pneumonia case and received multiple courses of antibiotics before presentation. CT of the chest was performed and showed a large right lung mass measuring 17×17×9.5 cm infiltrating the chest wall, with mild right pleural effusion. Laboratory tests at this time were all normal except for anemia (Hb=8.6 g/dl). CT-guided biopsy was obtained from the lung mass along with pleural fluid sample and sent for histopathological examination.

The results of the histopathology showed positivity of both tissue and fluid samples for malignant round cell neoplasm (solid sheets of small round cells with high nucleocytoplasmic ratio, focal spindling, and moderate vascularity). Immunohistochemistry was strongly positive for CD99 with negative TTF1, LCA, and pancytokeratin, which was compatible with the diagnosis of extraskeletal Ewing sarcoma (EES). Metastatic workup including CT of the abdomen, bone scan, and bone marrow biopsy was negative for distant metastasis.

The patient started alternating VAC–IE regimen with very good initial clinical response after first cycle and good radiological partial response on CT after the fourth cycle (the mass decreased in size by about 60% with complete disappearance of the pleural effusion).

However, after the sixth cycle, the mass had become stationary in size; at this time, thoracic surgeon was consulted for resection of the tumor and found the mass borderline resectable, and hence the patient received two more cycles of carboplatin AUC5 day 1 and etoposide 150 mg/m² days 1–3 with cycle repapered every 21 days. Thereafter, the patient was referred for surgical assessment once again (after about 30 weeks), where she underwent surgical resection (right middle lobectomy).

The histopathology examination of the mass showed no residual malignancy. The patient left the hospital after surgery without complications and she is still under regular follow-up at our hospital with no relapse until now (35.5 months).

Metastatic workup for both patients included CT (neck, chest, abdomen, and pelvis), bone scan, and bone marrow biopsy before treatment to rule out the possibility of metastasis and the presence of skeletal primary, and all were free from metastasis.

Discussion

Ewing sarcoma family/PNET is a group of aggressive sarcomas of the bone and less commonly soft tissues, characterized histologically by primitive small round cells of neuroectodermal origin that need immunohistochemistry staining to establish the diagnosis [1].

Primary pulmonary EES/PNET is an extremely rare tumor. The first case of primary pulmonary EES was reported in 1989 by Hammar *et al.* [4], and described in the study by Takahashi *et al.* [5], with about 10 case reports published around the world. It usually affects patients in the second decade of life with male predominance [5]. Our cases comprised two patients, one male and one female, having a median age of 20 years (range: 19–21 years).

The rarity of primary pulmonary PNETs necessitates detailed examination by clinical and radiological means to rule out metastatic tumor from an extrapulmonary primary site. The clinical picture is not specific. Most patients (90%) present with a

painful chest wall mass. Fever and malaise are commonly associated systemic manifestations [6]. Dyspnea, cough, chest pain, and malaise were the predominant presenting symptoms, with several months (range: 2–8 months) between complaint and diagnosis. Both cases received multiple courses of antibiotics for presumed pneumonia before diagnosis.

Imaging characteristics of EES family of tumors have been described in the literature [2,5,7,8]. Although characterization of pulmonary Ewing sarcoma has been limited, primary pulmonary Ewing sarcoma most commonly presents as a circumscribed solitary mass with heterogeneous appearance both on noncontrast and on contrast-enhanced CT. Occasionally, intralesional calcifications or an ipsilateral pleural effusion may be seen. Infrequently, a mass may demonstrate evidence of invasion of adjacent structures [7]. The main radiological finding in our cases was a large heterogeneous soft tissue lung mass on the right side in both patients.

Involvement of bone marrow, the hallmark of an osseous origin, is typically absent in CT or MRI in these extraosseous tumors [9]. None of our cases showed bone involvement on CT, or bone scan, and bone marrow aspiration was negative.

Ewing sarcoma family of tumors shares common morphological features of closely packed small primitive round cells [8], and hence it should be considered in any small cell neoplasm; they are characterized by strong continuous cell membrane expression of CD99 protein, and genetic translocation involving EWS in ~90% of cases [1]. Histological examination of samples taken from both patients revealed markedly cellular tumor composed of malignant round cells stained positive for CD99 and negative for TTF1, LCA, and pancytokeratin. The morphology and immunohistochemical results were consistent with the diagnosis of EES. Reciprocal chromosomal translocation t(11;22) (q24;q12) could not be studied because of lack of this test at our institution. Management of primary pulmonary EES/PNET usually needs aggressive multimodality treatment with upfront generous surgery followed by chemotherapy plus or minus radiotherapy [5]. The most effective drugs for the treatment of Ewing sarcoma family of tumors have proven to be ifosfamide, etoposide, cyclophosphamide, vincristine, doxorubicin, carboplatin, and actinomycin D. Dose intensification facilitates control of the disease and better chance of conservative surgery because of the high percentage of necrosis achieved [10]. The approach used in our patients was

aggressive systematic neoadjuvant chemotherapy to facilitate complete surgical resection after maximum chemotherapy response. Adding two cycles of carboplatin after six cycles of VAC–IE resulted in more objective response with an excellent pathological response that may suggest the favorable adding value of the carboplatin at the primary management instead of using it as a second-line chemotherapy.

Conclusion

Primary EES of the lung should be considered in the differential diagnosis when a young patient is presented with large lung mass without evidence of primary extrathoracic disease. Immunohistochemistry is compulsory to confirm the diagnosis. Such tumor needs integration of multidisciplinary team for early diagnosis and better management.

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Conflicts of interest

There are no conflicts of interest.

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