

Primitive Neuroectodermal Tumour of the Chest Wall—A Report of Two Cases and Review of Literature

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Abstract

Introduction: Primitive neuroectodermal tumours (PNETs) of the chest wall are rare entities and little is known regarding its biological activity and prognostic factors. Two cases are reported and the available literature reviewed to highlight the presentation and management of these tumours. **Clinical Features:** We report 2 patients who were diagnosed with PNET of the chest wall in our centre. As there are no clinical features or basic diagnostic measures which are characteristic of these tumours, diagnosis is based on special tests. With the advent of newer immunohistochemical methods, it is now diagnosed more confidently. **Treatment:** Both patients received multidisciplinary modalities of treatment, comprising extensive surgical resection, chemotherapy and radiotherapy. **Outcome:** One patient succumbed to the disease one year after diagnosis and the other is currently disease-free, both clinically and radiologically at 24 months. **Conclusion:** Despite multidisciplinary modalities of treatment, the prognosis of PNET is still generally poor. Early diagnosis and treatment are important to improve the chances of survival.

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Key words: Askin's tumour, Chest wall sarcoma, Homer Wright rosettes, Immunohistochemistry

Introduction

Tumours of the chest wall are uncommon and are usually sarcomatous in nature. Primitive neuroectodermal tumours (PNETs) are rare and are thought to arise from neuroepithelial cells, possibly derived from the peripheral intercostal nerves. They could also arise from the neural crest cells, which have migrated alongside the peripheral nerve. Askin et al¹ described the first series of 20 patients with PNET of the chest wall in 1979 in which the median survival was only 8 months. We report 2 cases along with a review of available literature to highlight the presentation and management of this rare condition.

Case Reports

Case 1

A 16-year-old female was admitted with symptoms of dyspnoea, cough and right-sided chest pain of a week's duration. She had no previous medical history of note

except for childhood asthma. Physical examination revealed absent breath sounds over the right lung base. A chest X-ray performed showed a soft tissue mass in the right chest wall associated with pleural effusion (Fig. 1). On contrast enhanced computed tomography (CT), performed after drainage of the effusion, this mass showed heterogeneous enhancement and had focal areas of low density compatible with areas of necrosis (Fig. 2). There was expansion of the sixth rib with a periosteal reaction but there was no mediastinal or hilar lymphadenopathy demonstrated. The pleural fluid analysis yielded an exudative picture and the cytology was consistent with PNET. Fine needle aspiration cytology (FNAC) of the mass confirmed the diagnosis. She underwent chemotherapy with 3 cycles of vincristine, adriamycin and cytoxan. Her symptoms improved and the tumour initially showed a 40% reduction in size but later became stable. As her residual disease was still extensive and measured 10 cm on the CT scan, surgical excision was planned. At surgery, the tumour was resected enbloc with

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Fig. 1. Chest radiograph showing the soft tissue mass with the associated pleural effusion.

the fourth to ninth ribs and a wedge of the middle and lower lobe of the lung. The chest wall defect was closed with Marlex mesh and bone cement. Histological examination confirmed a PNET (Fig. 3). Despite surgery and postoperative radiotherapy, she had a relapse 6 months later and presented with spinal cord compression from metastatic PNET to the lower thoracic and upper lumbar vertebrae. She underwent a decompression laminectomy of the tenth thoracic to the second lumbar vertebrae. Intraoperatively, there was tumour recurrence involving the bodies of T11–L2 as well as the paravertebral space around T12 which extended into the spinal canal, causing cord compression. On histology, metastatic PNET was confirmed. She received a further course of postoperative radiotherapy but finally expired about 2 months after the surgery.

Case 2

A 48-year-old Chinese man presented with a 6-month history of a right chest wall mass. He had initially noticed discomfort in the right side of his chest on ingestion of alcohol and subsequently noticed a palpable mass in the anterior chest wall. The chest radiograph showed a large mass in the right upper zone. On contrast enhanced scan, this heterogenous mass was shown to occupy the anterior portion of the right hemithorax, and extended through the chest wall to displace the pectoralis muscles. No associated rib destruction was demonstrated despite the size of the mass. A needle biopsy under radiological guidance was performed and small cell lung carcinoma was diagnosed. He underwent 6 cycles of chemotherapy consisting of etoposide and dexamethasone, with moderate reduction in the tumour size. An enbloc resection of the tumour along



Fig. 2. Computed tomographic scan showing the heterogenous density of the tumour and expansion of the adjacent rib with periosteal reaction.

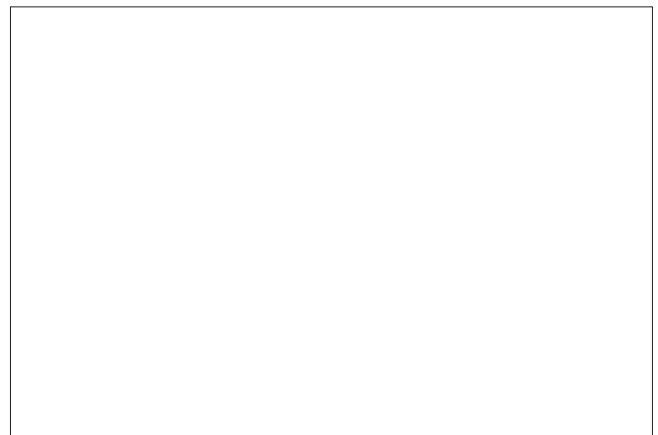


Fig. 3. Histology showing sheets of small round cells with dense nuclei and indistinct cytoplasm (Haematoxylin-eosin stain, original magnification $\times 400$).

with the first to third ribs was done and the chest wall defect was closed with a Marlex mesh and bone cement. On light microscopy, there were features suggestive of PNET, which was confirmed by immunohistochemistry. He is under regular follow-up and, at 24 months, is doing well with no clinical or radiological features of relapse.

Discussion

Peripheral neuroectodermal tumours of the chest wall are distinct clinicopathologic entities of uncertain histogenesis. They are characterised by malignant small round cell tumours of the thoracopulmonary region. This tumour, first described by Askin et al in 1979, had a poor prognosis despite aggressive multidisciplinary treatment and the median survival in their series was only 8 months. It is most often seen in children and adolescents although there are increasing reports of Askin's tumour in the adult population.² Presentation may be as insidious onset of pleuritic chest pain, shortness of breath or a palpable thoracic mass. Up to 50% of patients may already have metastatic disease at the outset, most commonly to the lungs and bone.³ Clinical examination may reveal a palpable

mass with or without significant pleural effusion. Metastatic disease to the vertebrae may result in neurological symptoms and signs due to spinal cord or nerve root compression.

Radiologically, these tumours show unilateral chest wall involvement with or without pleural involvement or rib destruction.^{4,5} On CT and MRI scans, they tend to be large and show a heterogeneous appearance attributed to haemorrhage and necrosis.⁵ Rarely, they may have areas of calcification.⁴ The appearances of the tumour on CT and MRI are therefore those of a large soft tissue tumour and there are no pathognomonic features. The large size of the tumour makes radiological assessment of pulmonary involvement unreliable and surgical assessment of the lung involvement necessary. CT scan helps to evaluate the extent of the local disease and its relationship with the surrounding vital structures so that surgical resection may be planned. A bone scan is performed to look for possible distant bone metastasis. Diagnosis is based on material obtained by core needle biopsy in most cases, often percutaneously, under radiological guidance.⁶ The close histological resemblance with other tumours gives rise to the many differential diagnoses, which makes the diagnosis of this tumour even more difficult.

Documentation of the pathologic spectrum of PNET is now well established. Generally, these tumours resemble neuroblastomas, being composed of sheets and lobules of small rounded cells with darkly stained nuclei. Cytoplasm is usually indistinct. In many tumours, there are structures resembling Homer Wright rosettes, where the cells are radially arranged around central cores that appear hyaline or fibrous. Classic Homer Wright rosettes are not always present. These tumours demonstrate immunohistochemical reactivity for neuron specific enolase and the cell surface antigen (p30/32) encoded by MIC-2 gene.⁷ The most characteristic ultrastructural feature is the presence of elongated cell processes that interdigitate with one another and contain small dense core (neurosecretory) granules.

Neuroblastoma, extraosseous Ewing's sarcoma, rhabdomyosarcoma and lymphoma form the differential diagnosis of a small round cell tumour of the chest wall in children or adolescents. Expression of MIC-2 gene product and beta-2 microglobulin is strong evidence that one is dealing with PNET or Ewing's sarcoma rather than neuroblastoma.⁸ Generally, a tumour is regarded as PNET rather than extraosseous Ewing's sarcoma if it contained well-defined Homer Wright rosettes, if there is evidence of neural differentiation ultrastructurally, or if two or more neural immunohistochemical markers (neuron specific enolase, Leu-7, synaptophysin, chromogranin) are present. A myxoid stroma, cells with cross-striations, positivity for muscle markers (desmin, muscle specific actin, myoglobin) and ultrastructural evidence of microfilaments distinguish

rhabdomyosarcoma from PNET. Leukocyte surface antigen will be positive in a lymphoma. Cytogenetics may reveal the presence of a reciprocal unbalanced translocation (11:21) in Askin's tumour.⁹

In all published series of PNET, there is a consistent poor outcome and prognosis noted.^{10,11} Most patients do not survive beyond a year and recurrence is common. A multidisciplinary approach is adopted for treatment and it is done preferably in specialised regional centres so as to attain experience in the management of this disease. Surgical option in the management of PNET is crucial for local control. In the Memorial Sloan-Kettering Cancer Centre's experience, it was found that complete remission was achieved in patients who received both surgery and chemotherapy, rather than from chemotherapy alone.¹⁰ Resection should be aggressive with the aim of achieving good margins of resection. This is particularly so in PNET as it has a striking tendency to recur locally.¹² In a retrospective analysis of 42 patients by Jurgen et al,¹² it was found that 10 out of the 12 relapses had only intralesional or marginal resection. However, it is difficult to achieve good margins of resection as the tumour is often extensive and in a difficult anatomical site. Therefore, neo-adjuvant chemotherapy is often given to shrink the tumour before resection and also to treat possible micrometastasis. Chest wall reconstruction is required to close the defect, most often with bone cement and Marlex mesh, which was done in our patients.

There is little information on the most efficacious chemotherapeutic regime in the treatment of PNET. The comparison of different chemotherapeutic regimes is restricted by the non-homogeneity of the groups with respect to number of patients, tumour sizes, local therapy procedures and the period of observation. PNETs were treated initially with the neuroblastoma protocol (which is cisplatin based) as both share similar neuroectodermal markers.¹³ However, when they were placed in the Ewing family of tumour in view of similar oncogenesis, the use of anthracyclines plus alkylating agents were introduced. It was found that regimes designed for treatment of Ewing's sarcoma appeared to be superior to those designed for neuroblastoma.¹²

The use of high dose chemotherapy with autologous bone marrow transplantation remains controversial. It was found that the use of high dose chemotherapy followed by either autologous bone marrow transplantation or peripheral stem cell rescue is of value in Ewing's sarcoma.¹⁴ Hence, this potential benefit may apply to patients with Askin's tumour, especially in patients with metastasis at presentation, as this group of patients has a poorer prognosis compared to those with localised disease. Young et al,¹⁵ in their series, reported an intensive regime comprising chemoradiotherapy

followed by bone marrow transplantation in their series of patients with sarcomas of the chest wall, including Askin's tumour. The preliminary results were good having a significant complete response rate (CR) with acceptable morbidity.

Classical Ewing's sarcoma is radiosensitive and there is no evidence to suggest that PNET should behave otherwise. Radiotherapy is given for radical control of the primary disease or as adjuvant therapy following resection. The dose for radical radiotherapy is usually between 50 to 60 Gy in daily fractions of about 1.8 Gy. Miser et al¹⁶ found, from their series of patients with PNET of the chest wall treated with 45 Gy to the tumour with a surrounding 2 cm margin, that there was no recurrence in the radiation field although 3 had pleural recurrence. The dose for adjuvant radiotherapy varies between 20 and 60 Gy. Radical radiotherapy is seldom used as the first modality for treating primary disease, as there is the fear of late second malignancy. It is adopted only when surgery would give a poor functional result. On the other hand, adjuvant radiotherapy is used when there is a high risk of recurrence such as residual microscopic disease, marginal resection and probable tumour contamination during surgery.

Summary

PNET of the chest wall or Askin's tumours pose a diagnostic and therapeutic challenge to clinicians and surgeons. Much is still unknown about its biological behaviour and the current treatment protocol is multidisciplinary in nature. While it is accepted that they are highly malignant tumour with poor prognosis, newer treatment protocols are being evaluated to guide treatment strategies in the future.

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