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From Ataxia to Diagnosis of Askin Tumor – a Case Report

Marko Bašković^{1,*}, Božidar Župančić¹, Mirko Žganjer¹, Igor Nikolić², Davor Ježek³, Lucija Čizmić⁴

ABSTRACT

Peripheral primitive neuroectodermal tumors (pPNET) are a group of extremely rare, aggressive, malignant tumors that are most often found in the thorax (Askin tumor), abdomen, pelvis, extremities and less frequently in the head and neck. The most important prognostic factor is the stage of the tumor. Significant progress both in surgery and in neoadjuvant and adjuvant chemotherapy and radiotherapy, as well as the improvement in diagnosis by cytogenetic and immunohistochemical analysis, should improve the survival rate. We report a case of a 14-year-old girl, with ataxic gait, cardiopulmonary compensated, without respiratory symptoms, who was referred to our hospital for further examination and treatment of newly discovered tumor of the left hemithorax. After a detailed radiological and laboratory investigation, next step was an extensive thoraco-neurosurgical surgery. After histopathological, cytological and molecular analysis, a diagnosis of Askin tumor was made.

KEYWORDS

Askin's tumor; peripheral primitive neuroectodermal tumor; ataxia; pediatric surgery

AUTHOR AFFILIATIONS

¹ Department of Pediatric Surgery, Children's Hospital Zagreb, Zagreb, Croatia

² Department of Thoracic Surgery, Clinical Hospital Dubrava, Zagreb, Croatia

³ Department of Histology and Embriology, University of Zagreb, School of Medicine, Croatia

⁴ University of Zagreb, School of Medicine, Zagreb, Croatia

* Corresponding author: Department of Pediatric Surgery, Children's Hospital Zagreb, Ulica Vjekoslava Klaića 16, Zagreb 10000, Croatia; e-mail: baskovic.marko@gmail.com

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INTRODUCTION

Primitive neuroectodermal tumors are groups of highly malignant tumors composed of small round cells of neuroectodermal origin. They show a great variety in clinical manifestations and a great cytological similarity to other small cell tumors, which through the past classification of this tumor group caused a series of controversies. Although Askin's tumor was first described in 1979 (1), only Batsakis et al. (2) the family of primitive neuroectodermal tumors divided into three groups; I. primitive neuroectodermal central nervous system tumor, II. neuroblastoma, III. peripheral primitive neuroectodermal tumor (pPNET – tumors that originate from tissues outside the central and autonomic nervous system). Peripheral primitive neuroectodermal tumors are also classified as part of Ewing's tumor family because they represent different manifestations of the same tumor and have similar genetic changes. Ewing's sarcoma is more common in bones, while peripheral primitive neuroectodermal tumors are more common in soft tissues. Immunohistochemical and cytogenetic studies indicate that these tumors have a common origin (known to share the same reciprocal translocation, most commonly between chromosomes 11 and 22), and therefore peripheral primitive neuroectodermal tumors are divided into the following groups; I. Ewing's sarcoma, II. malignant peripheral primitive neuroectodermal tumors (peripheral neuroepithelioma of bone and soft tissues), III. Askin's tumor (peripheral neuroepithelioma of the thoracopulmonary region), IV. other rare tumors (neuroectodermal tumor, ectomesenchymoma, peripheral medullary epithelioma) (3). Peripheral primitive neuroectodermal tumors have very often aggressive clinical behavior compared to other tumors that originate from small round cells of neuroectodermal origin. They are exceptionally rare with an annual incidence (in the age group from the age of 20 years) of 2.9 patients per million inhabitants. In recent major studies, peripheral primitive neuroectodermal tumors mostly occur in the second decade of life with slightly higher frequency in male populations. There are 4–17% of all soft-tissue tumors in the children's population and dominate in children of white race and Latino Americans origin (4).

CASE REPORT

A 14-year-old girl, born of proper pregnancy and childbirth, normal psychomotor development, regular personal and family anamnesis, came to the local hospital due to fatigue in her legs which appeared ten days ago. During the examination, the girl was afebrile, oriented in time and space, regular speech, cardiopulmonally compensated, without respiratory symptoms, with the asymmetry of the lips and ataxic gait. The thorax was asymmetrical with the protuberance of left hemithorax (Figure 1). The auscultatory finding on the heart was tidy, on the both lungs hearing breathing with the left apical rear silent breathing sound. The walk on the heels and fingers did not work, and she stood up adhering to table. She was unstable in Romberg. In the antigravitational position she had a trembling hand. The tetive muscular reflexes of the lower extremities were extended reflex zones. Skin reflections at all levels were not challenged. Head

CT, abdominal ultrasound and lumbosacral spine x-ray were initiated. Head CT and abdominal ultrasound were tidy while lumbosacral spine x-ray noticed soft tissue shadow of the left hemithorax, followed by initiation of chest x-ray by verifying the large shadow of the left hemithorax that suppressed the mediastinal structure contralaterally and compressed the pulmonary parenchymal caudally (Figure 2). The right lung was free of inflammatory and delayed changes. There was no pleural effusion. In the area of the 5th rib on the left was a visible lytic lesion susceptible to osteolysis. With the diagnosis of neoplasm of uncertain or unknown etiology, the girl was transferred to the Children's Hospital Zagreb for further treatment. It is initiated ECG, echocardiogram, thoracic ultrasound and CT, MR of neuroaxis and complete laboratory findings. The echocardiogram showed a fully accurate finding while the ECG recorded sinusoidal frequency 84/min, vertical electric axis (+92°), time intervals with repolarization disturbance. The thoracic CT was verified by a large, sharply restricted tumor formation of the left chest extending from the apical to the base at a length of 22 cm (Figure 3a), while spreading the volume of the thorax leading to the thoracic wall protrusion (Figure 3b). The tumor suppressed the mediastinal structures contralaterally without infiltrating them. The left bronchus was shown in the initial part, while it was later covered by tumor formation. Tumor formation was mixed characteristics of the inhomogeneous structure, partially filled with denser fluid content absorption coefficient between 20–30 HU, while in the back was predominantly intercalated with calcifications and fibrous elements. The back part of the fifth rib in the length of 50 mm was destroyed as well as the associated costovertebral joint. MR of neuroaxis at ThIV, ThV and ThVI levels showed intraspinal propagation of tumor of extradural position (Figure 4). Laboratory findings were within normal limits except for the following; sedimentation 75 (↗), lactate dehydrogenase 258 (↗), ferritin 156 (↗), NSE 20.2 (↗). On the third day, ultrasound was performed by percutaneous puncture biopsy through the third intercostal space in the posterior axillary line. The tissue cylinder referred to pathohistological and cytological analysis that did not find tumor cells. On the tenth day, a combined thoraco-neurosurgical surgery was initiated. The surgical procedure involved a left thoracotomy, full extirpation of a huge tumor spreading into the spinal canal, decompression laminectomy (ThIV–ThVI) and the 5th rib resection. The final diagnosis was obtained by a pathohistological, cytological and molecular analysis. The tumor was encapsulated, partly cystic, in a solid part with the necrosis. It was a tumor of small blue round cells constructed of diffuse proliferation of uniform cells of blastoid nuclei, gentle chromatin of scarce cytoplasm, with numerous apoptotic bodies and with 10 mitoses at 10 VF. Immunohistochemical, described tumor cells were vimentin, CD 99, and a smaller portion of NSE positive whereas only CKAE1/AE3, EMA and S100 were positive. The Ki67 proliferation marker was positive in 20% of tumor cells. RT-PCR determined translocation t(11; 22)(q24; q12) EWSR1/FLI1. Multiple times, chest x-ray indicated incomplete reexpand left pulmonary parenchyma which was also expected due to long compression (Figure 5). On the eighth postoperative day, the thoracic drain was replaced by a pleurostomia catheter connected to the Heimlich valve and a chemotherapy treatment with the VIDE (vincristine, ifosfamide, doxorubicin, etoposide) initiated according to EURO-E.W.I.N.G. 99 protocol.



Fig. 1 The patient with discrete prominence left hemithorax.

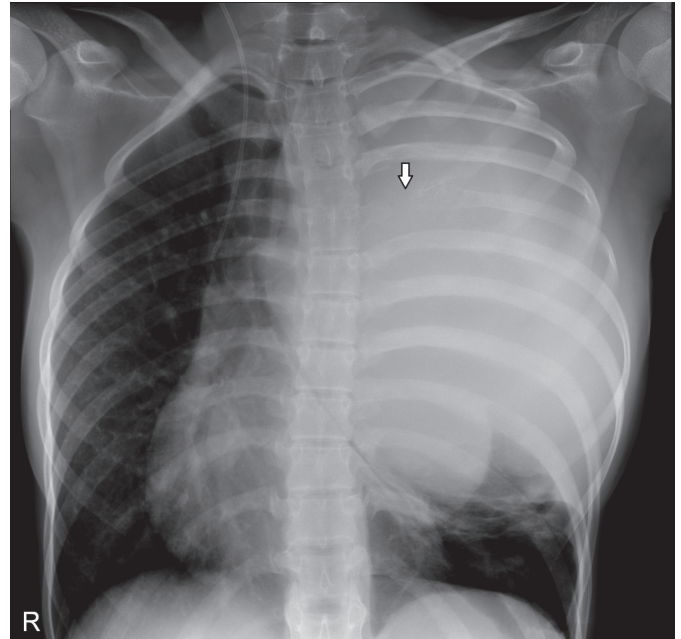


Fig. 2 Chest x-ray – a large soft tissue shadow of left hemithorax which suppresses mediastinal structures contralaterally and compresses the lung parenchyma caudally with subsequent subsegmental plate atelectasis. Osteolytic lesions of the 5th rib (marked with an arrow).

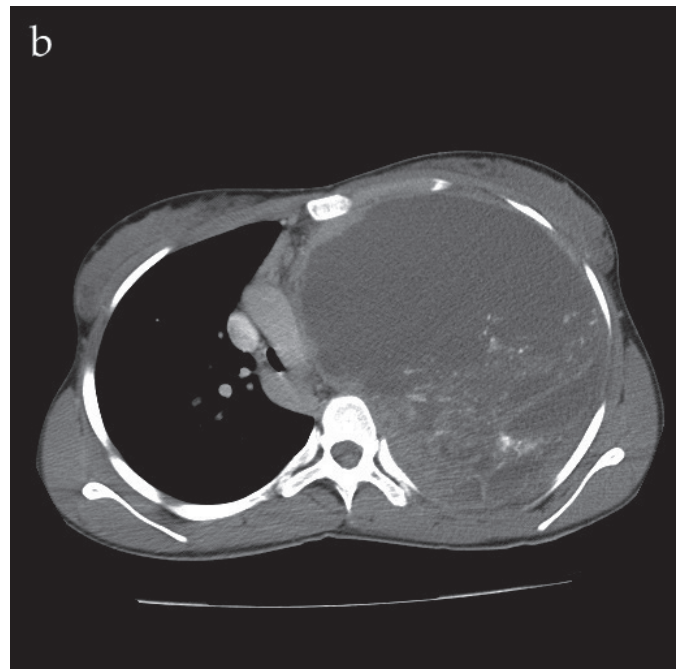
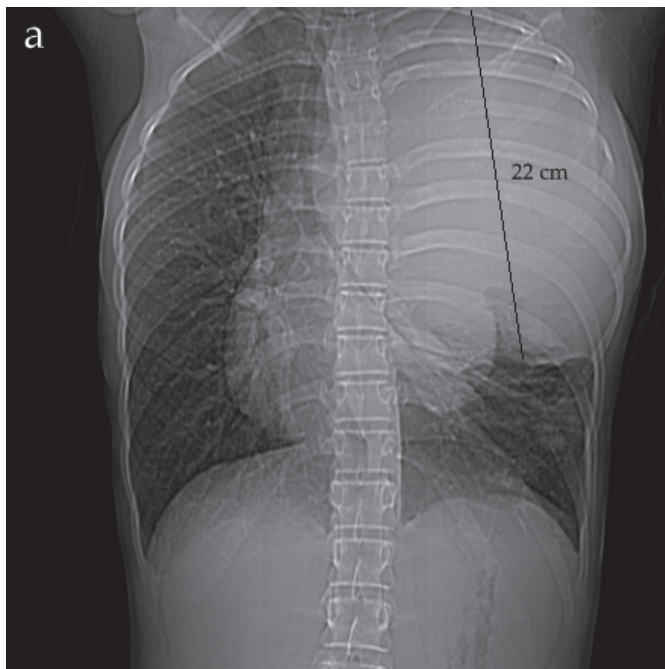


Fig. 3 Thorax CT (a – sharply limited tumor formation of the left chest that extends from the apex to the base in the length of 22 cm; b – transverse cross-section of the thorax showing the forward bulging of the thoracic wall).

DISCUSSION

By reviewing literature, most peripheral primitive neuroectodermal tumors are affected by thorax (Askin's tumor), pelvis, abdomen and extremities (5, 6, 7). Thoracic involvement is described in more than sixty cases. Interestingly, in the series of Jones and McGill tumor localization as

many as 11 out of 26 patients in the area of the head and neck (8). Clinical symptoms depend on the localization and on the stage of the tumor. It is interesting to note that the patient from our presentation had no symptoms of pain in the chest wall, dyspnea, cough, and weight loss as we can notice in other reports (9, 10). Ataxia, as the leading symptom, has not been recorded in any case so far. Literature as

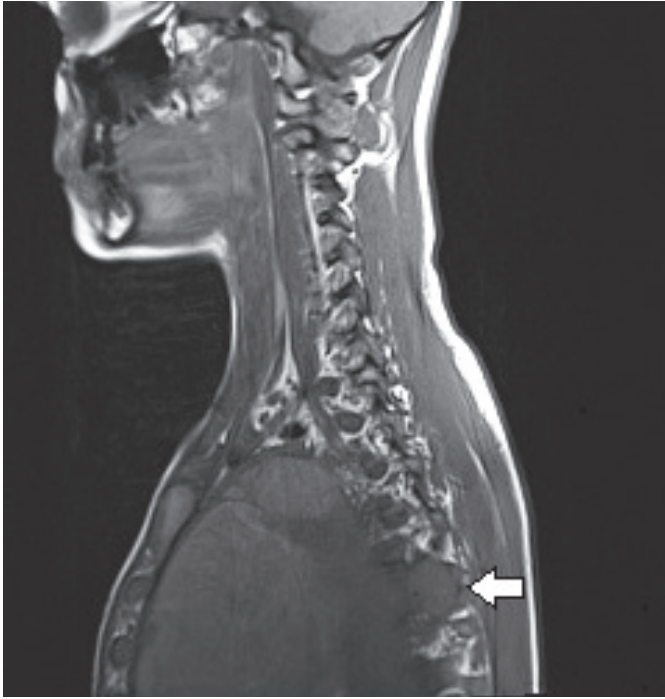


Fig. 4 MR of neuroaxis (sagittal section) – intraspinal propagation of the tumor process at the ThIV, ThV and ThVI level (indicated by the arrow).

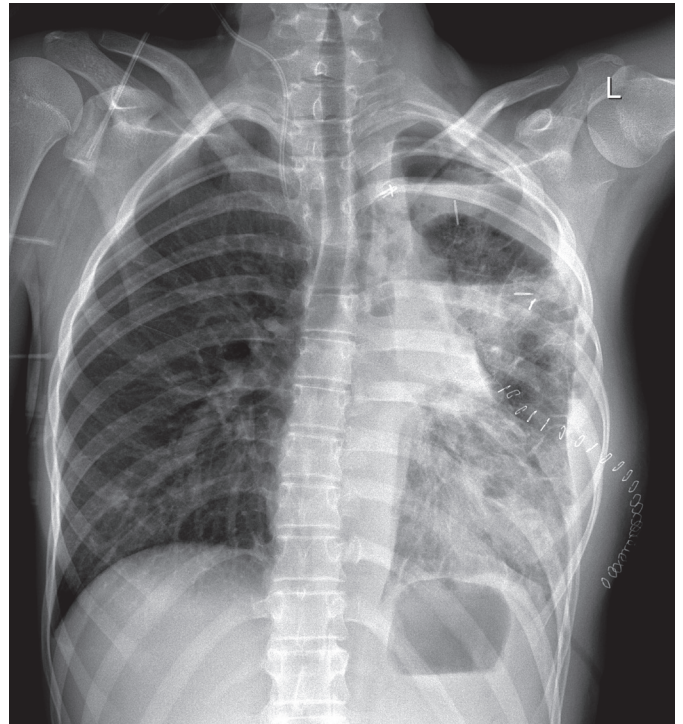


Fig. 5 X-ray of the lungs after the surgery – incomplete reexpansion of the lung parenchyma with resection of the 5th rib.

the leading cause of ataxia states the following conditions; central postinfectious and inflammatory causes, acute postinfectious cerebellar ataxia, postinfectious cerebellitis, ADEM, the clinically isolated syndrome, MS, spinal and peripheral postinfectious and inflammatory causes, Guillaine-Barré syndrome, Miller Fisher syndrome, Bickerstaff brainstem encephalitis, transverse myelitis, toxic ingestion (benzodiazepines, antiepileptics: carbamazepine and phenytoin, cough syrup: dextromethorphan, ethanol, marijuana), childhood stroke, intracranial bleeding, vertebral artery dissection, cerebellar venous infarction, meningitis, rhombencephalitis, labyrinthitis and celiac disease (11). In several large series of metastases, 21–30% of patients (lungs, bones, bone marrow) have been reported. The two-year survival rate is 28–38%, and five-year survival rate is only 14–17% (6, 12).

As far as tumor diagnostics are concerned, data obtained by light microscopy, cytogenetic analysis and immunohistochemical methods are of crucial importance in the definitive diagnosis of Askin's tumor. Based on histological studies alone, it is impossible to distinguish Askin's tumor from e.g. rhabdomyosarcoma, neuroblastoma or mesenchymal chondrosarcoma, where in all cases we find small, round, dark-colored cells. Electron microscopy in peripheral primitive neuroectodermal tumors reveals neurosecretory granules with microtubules and microfilaments. The final diagnosis by which peripheral primitive neuroectodermal tumors are distinguished from other small, round cell tumors and represented by most pathologists and cytologists is based on the immunohistochemical analysis of MIC2 (CD99) gene expression that produces an antigen (13). Recently, the immunohistochemical analysis of NKX2-2 gene product has become

increasingly important (8). There are other nonspecific markers that are also used in the diagnosis of this tumor group; S-100, vimentin, neuron specific enolase, CD75 and synaptophysin (14).

Radiology, primarily in the form of computerized tomography and magnetic resonance, definitely helps us to determine the limits of the tumor and the presence of metastasis. At CT, peripheral primitive neuroectodermal tumors primarily appear as heterogeneous masses, often infiltrating surrounding tissues. According to Ba et al. these tumors were hypodense, and osteolytic focal points were a sign that the tumor originated from the bone (15). Analogously to our radiological finding Xiao et al. as the main CT characteristics of these tumors described an irregular form (83.3%), heterogeneity (66.7%) and hypodensity (94.4%) (16).

As far as treatment is concerned, current guidelines are in favor of complete surgical resection (17). It is necessary, as far as possible, to completely remove the tumor, although this is not always possible with regard to the infiltration of vital structures. Chemotherapy and radiotherapy (adjuvant and non-adjuvant) are also key in treating this tumor. A review of literature is based on a series of protocols ranging from only two to six chemotherapeutics (18). Combinations used in the largest number of cases are doxorubicin, actinomycin D, cyclophosphamide, ifosfamide, vincristine, etoposide, busulfan, melphalan and carboplatin (VACA – vincristine, doxorubicin, cyclophosphamide, actinomycin, VAIA – vincristine, doxorubicin, ifosfamide, actinomycin, EVAIA – VAIA + etoposide; VIDE – vincristine, ifosfamide, doxorubicin, etoposide) (19). Carvajal and Meyers, with a comprehensive review of chemotherapy protocols and outcomes, recommended

the following regimen; vincristine, doxorubicin and cyclophosphamide with ifosfamide and etoposide (20). More recently, the use of adjuvant radiotherapy with doses greater than 60 Gy has been abolished since studies have shown that doses greater than 60 Gy are causing secondary malignancies. Kuttesch et al. reported that 20% of patients who received a dose greater than 60 Gy developed secondary malignant neoplasm (21).

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CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest.

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