CASE STUDY

PRINCIPLES OF DIAGNOSIS AND TREATMENT OF ASKIN'S TUMOR IN CHILDREN: CASE REPORT

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ABSTRACT

The aim of the study was to show principles of diagnosis and treatment of Askin's tumor in children. Diagnostic procedures include physical examination, chest X-ray, CT scan and PET CT, morphological, histological and immunohistochemical examinations, cytogenetic study. Primitive neuroectodermal tumors belong to the group of low differentiated, overly aggressive neoplasms, originating from cells of the parasympathetic autonomic nervous system. Patient F., 9 years old, first consulted by pediatric oncologist in 2014 with complaints of volume formation in the chest on the right side which progressively increases. Diagnosis: PNEP (primitive neuroectodermal tumor) of the soft tissues of the chest on the right side in the 4th intercostal space along the midclavicular line T2aN0M0, stage 2a, standard risk group. We've shown results of diagnostical process, treatment and it's result in our patient. Patients who have received combination therapy, including chemotherapy, surgical removal of the tumor and radiation therapy, have better prognostic results. However, relapses often occur that require more aggressive treatment with high-dose chemotherapy, monoclonal antibodies, and bone marrow transplantation.

KEY WORDS: Askin's tumor, children

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INTRODUCTION

Primitive neuroectodermal tumors (PNET) belong to the group of low differentiated, overly aggressive neoplasms, originating from cells of the parasympathetic autonomic nervous system. The incidence is about 4-17% of all soft tissue tumors in childhood. By origin, they are divided into peripheral PNET (pPNET), identical to Ewing's sarcoma, and central PNET (cPNET), which requires differential diagnosis with medulloblastoma, epindymoma, pinealoma, rhabdomyosarcoma, and neuroblastoma with primary brain damage [1]. In 1979, Askin first described 20 cases of PNET growing from the soft tissues of the thoracic area in children and adolescents, since then they have been called «Askin's tumor». These tumors in histological, immunohistochemical, cytogenetic and phenotypic similarity belong to the Ewing's sarcoma family, but are extremely rare [2,3].

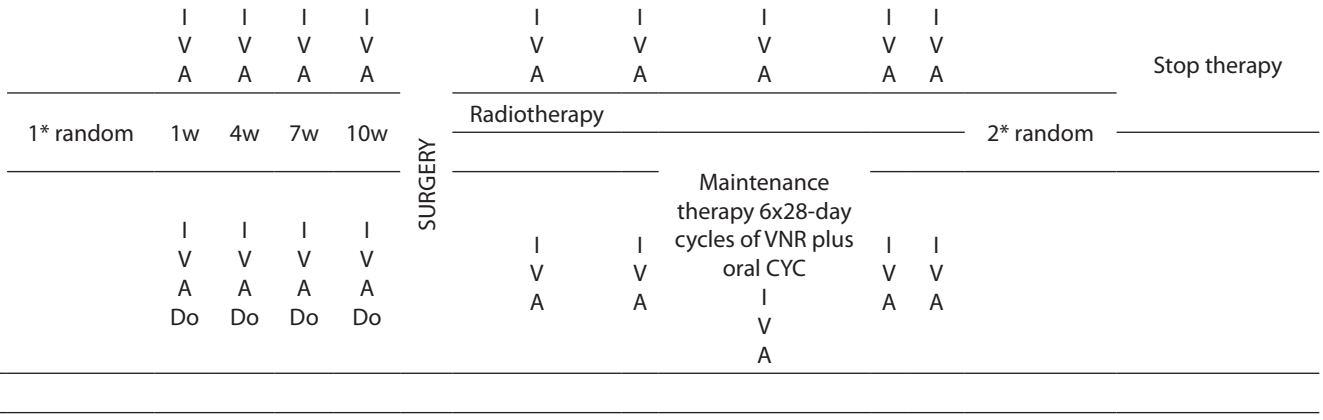
Diagnostic procedures include physical examination, chest X-ray, CT scan and PET CT, morphological, histological and immunohistochemical examinations, cytogenetic study. This tumor on palpation is slightly denser than the soft tissues of the chest wall, often there is destruction of the ribs, pleural effusion, which is visualized by chest radiography. However, it is necessary to perform CT scan of the thoracic and abdominal cavities and MRI of the chest wall to determine the size of the tumor, possible invasion of the lungs and the presence of distant metastases [3]. 26-28% of children have initially distant metastases and in about 30% of patients metastasis to the bone marrow is confirmed [4-6]. PET CT plays an equally important role in the detection of metabolically active tumors at the stage of primary diagnosis and to assess the response to treatment [4]. Morphologically, Askin's tumor is gray-white with necrotic, cystic and hemorrhagic areas in section. Histological examination reveals monomorphic small blue round cells, which probably originate from the neural crest [5]. Cytogenetic study in this case has an important diagnostic value. Thus, in 85% of cases there is a mutual translocation of t(11:22) (q24: q12) with the gene EWS-FLI-1. Checking presence of proto-oncogenes such as n-myc, c-myb, c-ets-1 and tumor markers (NSE, LDH) can be additional diagnostic criteria [7]. There are no PNET-specific markers, but CD99 is detected in most patients on immunohistochemical examination of tumor cell surfaces [8].

This tumor has rapid aggressive growth, frequent metastasis and progress during treatment. The prognosis is very poor. 2-year survival from diagnosis is less than 40%. Therefore, it is necessary to study new treatment strategies (chemotherapy, immunotherapy) in combination with autologous hematopoietic stem cell transplantation (auto THC) in order to improve the quality of life and survival of patients [9]. In their studies, Lascar S. and co-authors have shown that the best results are achieved with a combination of systemic (non-adjuvant and adjuvant) chemotherapy, surgical treatment and radiation therapy [10]. The first line of chemotherapy includes drugs such as vincristine, doxorubicin, cyclophosphamide, etoposide and ifosfamide [11, 12]. Frequent relapses and progression of the disease after first-line therapy required further research and the search for new treatment options that include cyclophos-

Table I. The result of immunohistochemical investigation

Markers	Present/absent
Monoclonal Mouse Anti-Human CD99. MIC 2 Gene Product Ewing`s Sarcoma Marker Clone 12B7 (Dako IS57)	"+"
Rabbit Monoclonal Antibody to Fli-1 (DBS RMPD025)	"+"
Monoclonal Mouse Anti0Human Cytokeratin Clone AE1/AE3 (Dako M3515)	"+"
Monoclonal Mouse Antibody to Human Leukocyte Common Antigen CD45	"-"
Monoclonal Mouse Anti- Human Neuron Specifie Enolase Clone	"-"
Monoclonal Mouse Anti-Human CD56	"-"
Polyclonal Rabbit Anti-S100 (Dako Z0311)	"-"
Monoclonal Mouse Anti-Myogenin Clone F5D (Dako IS067)	"-"
Monoclonal Mouse Antbody to MyoD1 Clone 5.2F (DBS PDM120)	"-"
Monoclonal Mouse Anti-Human Desmin Clone D33 (Dako M0760)	"-"
Monoclonal Mouse Anti-Human CD34 Class II Clone QBEnd 10 (Dako IS32)	"-"
Conclusion: according to the results of morphological and immunohistochemical studies, the phenotype characteristic of primitive neuroectodermal tumor (PNET).	

Table II. The European pediatric Soft Tissue Sarcoma Study Group (EpSSG) RMS 2005 study higt-risk localized rhabdomyosarcoma



phamide and topotecan, irinotecan and temozolomide in combination with high doses of ifosfamide. Nowadays, there are investigations for using of monoclonal antibodies, such as bevacizumab (Avastin) and sunitinib [13]. The long-term prognosis for Askin's tumor depends on the initial size, the presence of metastases, the level of LDH and combination therapy, namely surgery, chemotherapy and radiation therapy [14].

CASE REPORT

Patient F., 9 years old, first consulted by pediatric oncologist in 2014 with complaints of volume formation in the chest on the right side which progressively increases. He was hospitalized for additional examination and diagnosis. Results of the tests were performed:

- ultrasound of soft tissues (14.01.2014): tumor in the 2-4 ribs region, size 86 × 26 × 55 mm, with its own blood flow.
- CT scan of the chest and abdominal cavity with IV contrasting (15.01.2014): soft tissue tumor formation 81 × 58 × 25 mm (tumor volume is 62 cm^3) in the thickness of the chest wall; distant metastases to the chest, abdomen and retroperitoneal space were not detected (fig. 1).

Trepan - tumor biopsy, trepan bone marrow biopsy from 3 points and liquid bone marrow (20.01.2014). Tumor histology showed PNEP. Bone marrow without signs of damage. The result of immunohistochemical investigation present in table I.

Diagnosis: PNEP (primitive neuroectodermal tumor) of the soft tissues of the chest on the right side in the 4th intercostal space along the midclavicular line $T_{2a}N_0M_0$, stage 2a, standard risk group.

The child began treatment according to the CWS 2006 protocol on February 10, 2014.

The central venous port system was set up on March 4, 2014. After the 2nd block of chemotherapy, the tumor was not clinically determined. Control CT scan of the chest with IV contrast was performed on April 17, 2014: Residual tumor is not determined. Continuation of treatment according to the protocol on the line «complete response».

Treatment included 9 blocks of chemotherapy and radiation therapy of 40 Gr per pre-therapeutic volume of

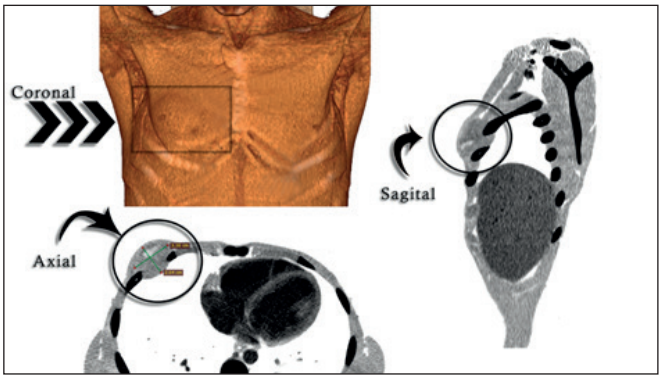


Fig. 1. CT scan of the chest and abdominal cavity shows soft tissue tumor

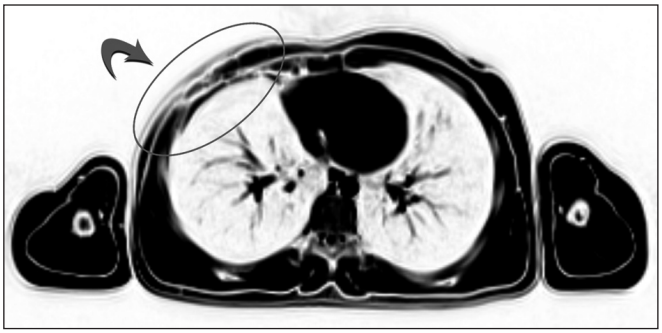


Fig. 2. Post operating seroma of the right sectoral area with perifocal fibrous post operating changes on CT

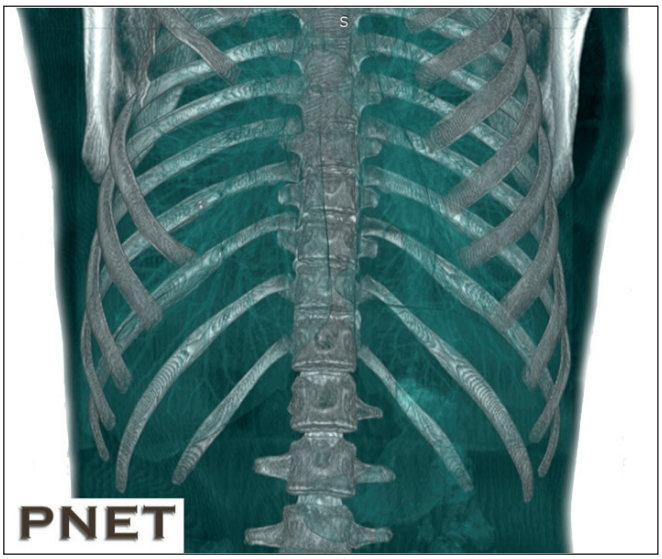


Fig. 3. Control contrast chest CT scan shows remission

the tumor (anterior surface of the chest on the right side). After this treatment child was include into the observation group (3rd clinical groups). Regularly passed routine examinations, including contrast CT scan of the chest and abdominal cavity, contrast MRI of soft tissues of the chest every 3 months. According to the results of examinations, no pathological changes were detected.

On December 6, 2016 (2 years of remission) child came for an examination with complaints of pain and the presence of a voluminous formation of the chest on the right side along the midclavicular line, and increase body temperature to 37.1C. Patient was hospitalized for further examination with diagnosis: the first recurrence of PNET?

Surveys were conducted:

Scintigraphy with radiopharmaceutical drug (9.12.2016): accumulation of the drug in the area of the head and upper third of the left femur - 280%.

Contrast CT scan of the chest (12.12.2016): additional volume formation of the anterior chest wall on the right side at the level of the anterior segments of 4 - 5 ribs on the right along the mid-clavicular line.

Surgical intervention was performed (15.12.2016): open biopsy of the tumor, trepan – biopsy of the bone marrow from the iliac crests and collected liquid bone marrow.

Extract from the investigation protocol: access over the three-dimensional formation along the midclavicular line in 4 intercostal spaces up to 3 cm, soft tissues are dissected in layers, revealed: two formations, one of which is covered with a hard fibrous capsule, the other next to the capsule - excisional biopsy of both formations.

The results of histological examination:

Tumor: growth of primitive neuroectodermal tumor (both samples)

Histological examination of the bone marrow: signs of depletion of all hematopoietic sprouts and fibrosis

Cytological examination of bone marrow: cellularity is slightly reduced, normoblastic type of hematopoiesis. When counting at low magnification about - 3 megakaryocytes.

Diagnosis: PNEP (primitive neuroectodermal tumor) of the soft tissues of the chest on the right side in the 4th intercostal space along the midclavicular line $T_{2a}N_0M_0$, stage - 2a, standard risk group. The first relapse.

The 2nd line of chemotherapy was started (table II). 2 blocks of therapy with etoposide, carboplatin, cyclophosphamide were performed as a mobilization course for the purpose of collection of autologous peripheral blood stem cells. A collection of material for autologous bone marrow transplantation was performed, but was unsuccessful due to severe aplasia.

The medical commission decided to carry out radical surgery, given the ineffectiveness of chemotherapy. Radical removal of the tumor with resection of IV and V ribs was performed on March 7, 2017. Plasticity of defect by a propylene grid, drainage of a pleural cavity and soft tissues were made. Post operating period gone without complications.

Histology: the growth of PNEP. After the operation child received 2 more chemotherapy blocks. After this treatment child had a remission and was include into the observation group.

20.09.2018 child came for routine examination with a suspicion of relapse. Surgical intervention was made (26.09.18): removal of a tumor on the right side of the chest.

There were 6 samples of the tumor resection edge:

№1 – the centers of growth of a malignant undifferentiated tumor among fibromuscular tissue;

№2 – fibrous - adipose tissue without signs of malignant growth;

№3 – fibrous - adipose tissue with hemorrhages, slight inflammation;
№4 – muscle tissue without signs of malignant growth;
№5 – muscle tissue without signs of malignant growth;
№6 – fibrous - adipose tissue without signs of malignant growth.
Trepan - biopsy of the bone marrow: the bone marrow is represented by red and yellow in a ratio of 1: 1. Red normocellular represented by all three sprouts with a predominance of granulocyte.

Morphological examination of the bone marrow (26.09.18): the cellularity of the bone marrow is reduced. Normoblastic type of hematopoiesis. 7 megakaryocytes were found at low magnification in a smear.

Contrast CT scan of the chest and abdominal cavity (05.10.18): picture of the condition after resection of the 4th - 5th ribs and soft tissues on the right side of the chest wall, accumulation of fluid in the soft tissues of the anterior chest wall on the right - surgical changes. Pneumofibrosis on the right D4 and D5. Single stable nodules D6,8. MRI of the chest with intravenous contrast (08.10.18): condition after combined treatment of PNET of the right sector. Post operating seroma of the right sectoral area with perifocal fibrous post operating changes (Fig. 2)

After surgery child received 3 courses of chimotherapy (Irinotican - Temodal).

PET/CT scan (19.02.2019): no signs of pathological radioactive pharmaceutical drug accumulation were detected. Fixation of radioactive pharmaceutical drug in a scar in soft tissues of a chest wall is more characteristic to after therapeutic changes as there are no convincing data for additional tumor with local accumulation of radioactive pharmaceutical drug. There is no convincing evidence for the presence of radioactive pharmaceutical drug active malignant process. Control of contrast CT scan of the chest (06.09.2019)(fig. 3). Remission continues.

PNET belongs to a group of highly aggressive malignant neoplasms, the histological substrate of which are small undifferentiated neuroectodermal cells [13]. Askin's tumor belongs to the group of peripheral PNET with primary lesions of the chest. It is often localized in the paravertebral areas [15]. Small cell sarcomas are a heterogeneous group of malignant neoplasms that remain diagnostically complex due to similar morphological and immunohistochemical characteristics. They are more often diagnosed in adolescents and young adults and have a prognostic course [16].

For this tumor, there are typical morphological features such as the presence of small cells with Homer-Wright rosettes. In immunohistochemical study positive CD 99. The presence of translocation t (11; 22) (q24, q12) and proto-oncogenes c-myb, n-myc, c-ets-1, which are important diagnostic criteria [7]. A significant increase in the level of LDH, relative to reference values, is considered a poor prognostic factor [19]. Usually this neoplasm recurs locally, but separate metastases can be detected [17]. This tumor is very rare and too aggressive, so the searching for new treatments that will improve the long-term prognosis is going all the time. Combined treatment involving surgical removal of the tumor with extensive resection of the edges in combination with chemotherapy (ifosfamide, vincristine, etoposide, D-actinomycin, doxorubicin) and radiation therapy has been shown to give better prognostic results and reduce the frequency of 3 recurrences [18].

CONCLUSIONS

Patients who have received combination therapy, including chemotherapy, surgical removal of the tumor and radiation therapy, have better prognostic results. However, relapses often occur that require more aggressive treatment with high-dose chemotherapy, monoclonal antibodies, and bone marrow transplantation.

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