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## Case Report / Приказ случаја

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### Extraskeletal Ewing sarcoma in the anterior abdominal wall

Екстраскелетни Јуингов сарком у предњем трбушном зиду

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## Extraskeletal Ewing sarcoma in the anterior abdominal wall

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#### SUMMARY

**Introduction** Extraskeletal Ewing sarcoma (ES), is highly malignant neoplasm occurring most commonly in the thoracic wall and paravertebral region. ES belongs to the group of small round cell tumors and displays pathognomonic structural abnormalities of *EWS* gene.

The aims of this article was to present extraskeletal ES in extremely rare anatomic location, an unusual clinical presentation, and modified treatment strategy.

**Case outline** A 15-year-old boy was admitted to the hospital with acute abdominal pain in the right iliac region. During urgent operation, because of suspected appendicitis with periappendicular infiltrate, partly haemorrhagic tumor tissue was discovered in the preperitoneal space. Histopathological and immunohistochemical analyses revealed tumor resembling extraskeletal ES. Postoperative CT scan has shown the tumor rest, which was completely removed in the second operation. The molecular genetic analysis confirmed extraskeletal ES by finding of the *EWSR1-FLII* fusion gene. Chemotherapy and radiotherapy according to VAC protocol were started, and the patient is free of the disease eight months after the first operation.

**Conclusion** Our case is the fourth case of extraskeletal ES located in the abdominal wall, the second case confirmed by molecular genetic finding, and the first case described in children at this anatomic location. Due to extremely rare location, unusual clinical presentation, and needed genetic analysis, the strategy of tumor treatment was modified with the good short-term result.

**Keywords:** extraskeletal Ewing sarcoma; primitive neuroectodermal tumor; soft tissue; abdominal wall; surgery

#### САЖЕТАК

**Увод** Екстраскелетни Јуингов сарком (ЈС) је веома малигна неоплазма која се најчешће развија у зиду грудног коша и паравертебралној регији. Спада у групу тумора малих округлих ћелија са патогномичном структурном абнормалношћу гена *EWS*.

Циљ овог рада је да прикаже случај екстраскелетног ЈС са изузетно ретком локализацијом, необичном клиничком презентацијом и модификованом стратегијом лечења.

**Приказ болесника** Дечак стар 15 година примљен је у болницу због акутног абдоминалног бола у десној илијачној регији. У току хитне операције због сумње на апендицитис са периапендикуларним инфилтратом, у преперитонеалном простору је нађено делимично хеморагично туморско ткиво. Патохистолошка и имунохистохемијска анализа указале су на вероватни екстраскелетни ЈС. Постоперативна КТ указала је на локални остатак тумора, који је комплетно одстрањен другом операцијом. Молекуларно-генетичким налазом фузионог гена *EWSR1-FLII* потврђена је дијагноза екстраскелетног ЈС. Лечење је настављено хемиотерапијом и радиотерапијом по VAC протоколу и осам месеци након прве операције код пацијента нема знакова рецидива болести.

**Закључак** Екстраскелетни ЈС у предњем трбушном зиду код нашег пацијента представља четврти случај ЈС на тој локализацији приказан у литератури, од тога други случај са дијагнозом потврђеном молекуларно-генетичком анализом и први описан у дечјем узрасту. Због екстремно ретке локализације, необичне презентације и неопходне генетичке анализе, стратегија лечења тумора је модификована са добрим краткорочним резултатом.

**Кључне речи:** екстраскелетни Јуингов сарком; примитивни неуроектодермални тумор; мека ткива; трбушни зид; хирургија

#### INTRODUCTION

Ewing sarcoma (ES) is an uncommon neoplasm, with an incidence reported at 1 to 3 per million people per year, mainly appearing in patients younger than 20 years, with peak incidence during the second decade of life. After osteosarcoma, ES is the second most common bone sarcoma in children and young adults, with slight male predominance. About 10%-20% of cases arise in extraskeletal sites, most commonly in the soft tissue of thoracic wall, paravertebral region, lower extremities, head, neck, and pelvis [1, 2].

ES belongs to a group of small, round cell tumors. It shows a varying degree of neuroectodermal differentiation, and typically demonstrates diffuse membranous

immunohistochemical CD99 positivity. The cells of origin of ES are either neural crest-derived stem cells or mesenchymal stem cells. Most of the ES harbor a somatic reciprocal chromosomal translocation, t(11;22)(q24;q21), that results in pathognomonic fusion of *EWSR1* to *FLI1* genes, generating the EWSR1-FLI1 oncoprotein. In about 15% of ES, *EWSR1* gene can be involved in alternative translocations with *ERG*, *ETV1*, *ETV4*, or *FEV* genes [1, 2].

The term ES comprises tumor entity formerly differentiated into classical bone ES, Askin's tumor of the chest wall, and peripheral neuroectodermal tumor (PNET). Formerly, PNET was defined as ES with more prominent neural differentiation, predominant extraskeletal location, and closely related with central nervous system PNETs [2, 3]. This is why some authors still use the term ES/PNET for this group of neoplasms.

The aims of this work was to present a case of a 15-year-old boy with extraskeletal ES/PNET in extremely rare anterior abdominal wall location, unusual clinical presentation and modified strategy of treatment.

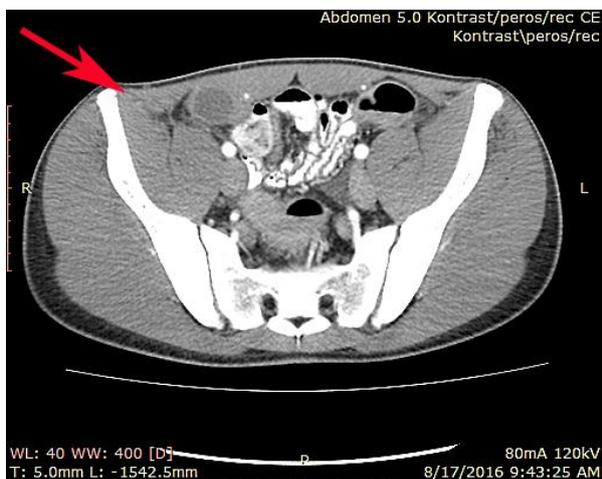
### CASE REPORT

A 15-year-old boy was admitted as an emergency to our department with acute abdominal pain that started a day before after he took part in a football match. There was no clear evidence of trauma. Clinical examination revealed a painful mass in the right iliac region. Ultrasound examination confirmed the existence of well localized hyperechogenic mass, with smaller hypoechogenic zones inside, measuring 50x40 mm, without internal color doppler signal, that could resemble periappendicular infiltrate. There were neither any changes in abdominal organs nor enlarged lymphatic nodes. Abdominal plain radiography was normal. Moderate leucocytosis ( $12.6 \times 10^9/L$ ) was present, and all other standard haematological and biochemical analyses were within the normal range. The patient had no previous diseases, and there were no significant data in the family history, including the absence of malignancies.

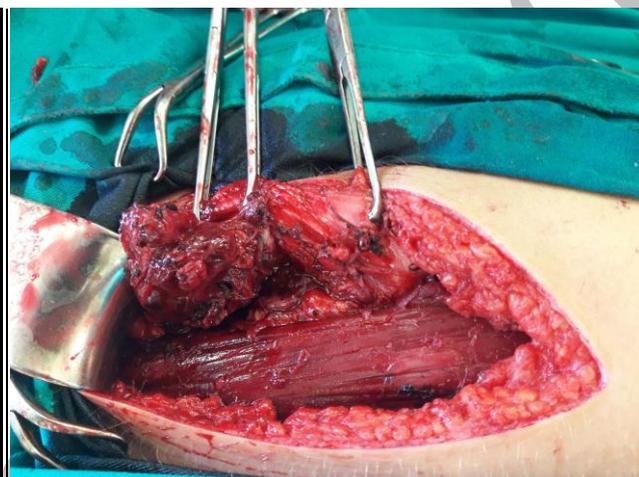
Because of the persistence of the right iliac tenderness, with the suspicion of periappendicular inflammatory infiltrate, the same day the patient was operated on, using McBurney incision. After the division of muscular layers, in the preperitoneal fat tissue, a large amount of mushy semiliquid haemorrhagic masses with tissue parts appeared. The visible mass was removed and sent to histopathological (HP) examination. There was a clinical suspicion of an old abdominal wall haemathoma, considering the patient's intense sports activities (football training and matches). Microbiological culture of the tissue revealed no growth of microorganisms. The patient's recovery was uneventful.

HP examination revealed necrotic tissue, with inflammatory component and haemorrhage, but parts of viable tumor tissue also were found. Small round tumor cells were hyperchromatic with a lack of cytoplasm, forming pseudorosettes, and showing numerous mitoses and apoptoses.

Immunohistochemistry revealed strong positive membranous staining for CD99, partly on vimentin and sporadically on synaptophysin, and negative staining for the leukocyte common antigen, desmin, myogenin, epithelial membrane antigen, CD68, chromogranin, and Wilms tumor-1 antigene (WT-1). Results of immunostaining with anti-FLI1 antibody was assessed as unreliable. Pathologists' conclusion was that mostly necrotic small round cell malignant tumor has immunohistochemical characteristics which mostly indicate ES/PNET. It was emphasized that genetic analyses are necessary for accurate definitive diagnosis. The tissue sample was sent to a foreign medical institution for these analyses. It took a relatively long time to get the genetic results. In the meantime, computed

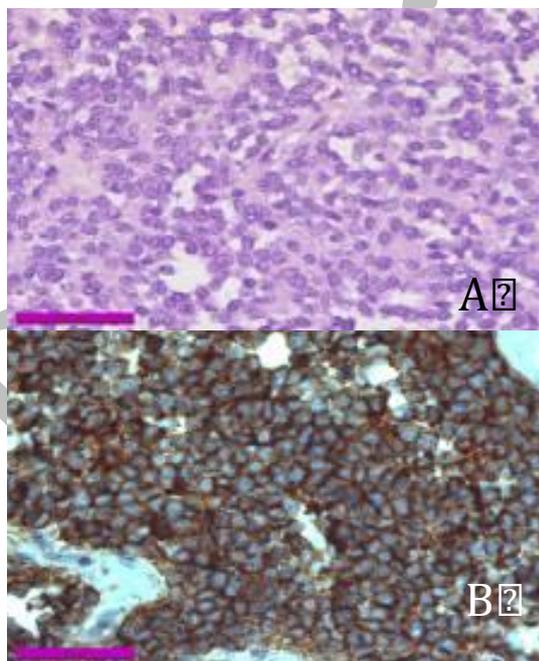


**Figure 1.** CT finding of the tumor in the abdominal wall.



**Figure 2.** Intraoperative finding of ES/PNET beyond rectus abdominis muscle.

tomography (CT) scan has shown a partly solid, partly cystic heterodense mass 3.8x2.6x3.7 cm beside and beyond the right rectus muscle. There were no changes neither in intraperitoneal lymphatic nodes



**Figure 3.** Microscopic feature of the tumor tissue. A. Typical characteristics of the small round cell tumor of childhood. B. Intense CD99 immunopositivity of all tumor cells indicating the extraskeletal Ewing sarcoma.

and abdominal organs nor in the thoracic cavity (Figure 1). A new operation was undertaken. A partly colliquated tumor, measuring 4 cm, was found close to the rectus abdominis muscle, not infiltrating the muscle, but infiltrating the underlying peritoneum (Figure 2). The whole tumor was removed with underlying peritoneum. It was obvious that the tumor generated from preperitoneal fat tissue. The recovery was uneventful. The new HP analysis confirmed the high probability of ES/PNET, and the reverse transcriptase polymerase chain reaction (RT-PCR) analysis of the tumor specimen have confirmed the *EWSR1-FLI-1* transcript, so the diagnosis of extraskeletal ES in the anterior abdominal wall was proved (Figure 3). The tumor process was classified

as the second stage. The boy received six courses of chemotherapy according to CWS protocol from 2012, consisted of ifosfamide, vincristine, and adriamycin and now is on radiotherapy regimen. The patient has neither clinical nor CT scan evidences of tumor recurrence or metastatic spreading eight months after the initial surgical treatment, but the further follow-up will show the overall result of the treatment.

## DISCUSSION

Histopathological aspect, immunohistochemical profile and, especially, genetic finding of *EWSR1-FLI-1* fusion gene far indicate extraskeletal ES in our patient. Some cases of ES have been reported in patients between 14 months and 77 years of age, but peak incidence is during the second decade of life, as was in our patient [1,2].

Anatomic location of extraskeletal ES in the preperitoneal fat tissue of the abdominal wall in our patient is exceptionally rare, considering that the most common locations of this highly aggressive neoplasm are thoracic wall, paravertebral region, lower extremities, head, neck and pelvic region [1,2]. However, in the literature there are several case reports or small series of extraskeletal ES/PNET with primary location in the kidney, lung, pancreas, uterus, urinary bladder, ovary, testis, parotid gland, mesenterium, skin and subcutaneous tissue [4,5]. After extensive literature search on the PubMed, using key words “Ewing sarcoma”, “primitive neuroectodermal tumor”, and “abdominal wall”, we found only three cases of neoplasms in this primary location [6,7,8]. Another three cases of extraskeletal ES in the abdominal wall location were reported, but all of them were described to be tumors confined to the subcutaneous adipose tissue [4,9,10], so we consider that they should not be included in the group of abdominal wall neoplasms.

To the best of our knowledge, the first case of extraskeletal ES in the abdominal wall was reported by Aydinli et al. in 2006. They described a 65-year-old male patient with painless mass, measuring 5 cm in the diameter, in the left upper quadrant of the abdominal wall, infiltrating the left rectus muscle. After probably complete tumor resection, the chemotherapy was carried out including vincristine, doxorubicin, cyclophosphamide, and etoposide for six cycles, and the patient had no evidence of tumor recurrence during one-year follow-up [6]. The second case was extraskeletal ES with the largest diameter of 6.5 cm, involving the left anterolateral muscle group of the abdominal wall in a 35-year-old woman. After the diagnostic incisional biopsy, neoadjuvant chemotherapy was started including vincristine, cyclophosphamide and adriamycin for three cycles. Because of poor response to chemotherapy, surgery was required, but authors did not report data of follow-up [7]. Roncati et al. in 2015. reported a third case of small extraskeletal ES/PNET measuring 1.5 cm, located in the subcutaneous tissue with deep muscle infiltration, appearing in a 45-year-old man. After elemental microanalysis, the authors described findings of a heavy metal bioaccumulation into the tumor cells, correlating with the chronic exposure to a transdermal delivery of heavy metal salts during local therapy of the irritated skin. Common *EWSR1-FLI-1* translocation was also found, and

after complete tumor excision and chemotherapy, the patient was without tumor recurrence one year after surgery (8).

Our case is the fourth case of extraskeletal ES located in the abdominal wall, the second case confirmed by the molecular genetic finding of characteristic structural abnormality of the *EWS* gene on 22q12, and the first case described in children in this anatomic location.

Extraskelital ES/PNET has a high malignant potential. Kushner, on a series of 43 patients without distant metastases at the time of diagnosis, reported the tumor recurrence rate of 25% during the first 24 months. Another 11 patients had metastases at the time of the diagnosis [11]. Kimber, on a series of 26 patients, reported an overall survival rate of 42% [12], while Zimmermann reported survival rate of 53% on a series of 13 patients [13]. Sarkar and Bähr made a meta-analysis and reported an overall number of 102 patients with Askin tumor, with a mortality rate of 41%, and the recurrence rate of 14% in the follow-up period in survivors [14]. The treatment of ES/PNET consists of surgery, chemotherapy [15, 16] and radiotherapy [16,17,18]. There are controversies in the literature about the timing of the operative treatment, but nowadays the majority of authors prefer pre-operative chemotherapy, with tumor regression in up to 95% of cases, enabling surgeons a radical tumor excision, without spilling and disseminating of tumor cells. The initial surgery, if undertaken, must not be mutilated or too risky if the tumor infiltrates adjacent organs or vascular structures [15,16,17]. We believe that initial surgery should be performed and the tumor removed, if imaging methods indicate that adjacent organs are not infiltrated, as was in our patient. Even after successful radical surgery, postoperative chemotherapy and radiotherapy must be performed, because extraskeletal ES/PNET carries the great risk of local recurrence and distant metastases. The operation must be performed even if preoperative chemotherapy has achieved complete tumor regression, in order to remove scattered viable malignant cells [12].

In our patient extraskeletal ES located in the preperitoneal fat tissue, manifested by spontaneous pain and tenderness on the exam in the right iliac region, the symptom and sign quite unusual for malignant tumors. The initial operation had been performed under suspicion of acute abdominal disease, i.e. for acute appendicitis with periappendicular infiltrate formation. The second operation was undertaken before the chemotherapy regimen started, because of the delay in getting molecular genetic analysis needed for the accurate diagnosis. The standard therapy protocol could have been changed because imaging analyses indicated the possibility of radical surgery.

In this paper the extremely rare case of extraskeletal ES with primary location in the abdominal wall is presented. The regimen of therapy was modified due to the atypical clinical presentation of the disease and the delay in getting the result of genetic analysis.

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