

Ewing's sarcoma

by Sony Sutrisno

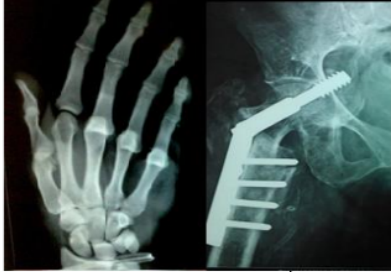
Submission date: 10-Feb-2021 05:39PM (UTC+0700)

Submission ID: 1506185122

File name: 6-2-47-480.pdf (505.33K)

Word count: 2535

Character count: 14481



International Journal of Orthopaedics Sciences

E-ISSN: 2395-1958
P-ISSN: 2706-6630
IJOS 2020; 6(2): 546-549
© 2020 IJOS
www.orthopaper.com
Received: 12-02-2020
Accepted: 14-03-2020

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Ewing's sarcoma of proximal humerus: A rare case report

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DOI: <https://doi.org/10.22271/ortho.2020.v6.i2i.2095>

Abstract

Ewing's sarcoma is a highly malignant small round cell tumor from bone or soft tissue. The clinical manifestation is non-specific, with local pain being the most common symptom by far. It affects prevalently among children younger than ten years. The chromosomal translocation t(11;22)(q24;q12) is one of the causes of Ewing's sarcoma. The gold standard diagnostic is incisional biopsy, additionally with cytogenic immunohistochemical. The current standard treatment for resectable Ewing's sarcoma begins with neoadjuvant chemotherapy, followed by limb salvage procedure and postoperative adjuvant chemotherapy. After resection of Ewing's sarcoma, the large bone defects should be reconstructed to restore the function of the affected limbs. The main options for reconstruction include autogenous bone grafts and endoprosthesis. Prognosis of Ewing's sarcoma is highly dependent on clinically evident metastatic disease, which may be preventable with early detection and treatment with aggressive local disease control and systemic multidrug chemotherapy. This article presents a rare case of an 8-year-old elementary schoolboy, diagnosed with Ewing's sarcoma of the proximal left humerus that was confirmed by plain radiograph and immunohistochemical biopsy. Patient's family discontinued the chemotherapy schedule and ignored the surgical reconstruction procedure.

Keywords: Ewing's sarcoma, malignancy, humerus, sarcoma, childhood age

Introduction

Ewing's sarcoma (ES) is a highly malignant small round cell tumor that occurs from bone or in soft tissue [1]. James Ewing firstly described Ewing's sarcoma as an endothelioma of bone in 1921 [2]. It is a common malignancy of bone in patients' childhood age or younger than 30 years of age. Ewing's sarcoma is more commonly seen in the appendicular skeleton and typically involves the femur, tibia, humerus, or fibula. As for location within long bones, the mass is almost always metaphyseal or diaphyseal with a percentage of 33% mid-diaphysis, 44% metadiaphysis, 15% metaphysis, and very rarely as much as 1-2% involves epiphysis [3]. A previous study reported that the long term survival rate is ranging from 60-70% with the current treatment by using neoadjuvant chemotherapy, followed by wide excision surgery, and then adjuvant chemotherapy [4]. The incidence varies among different racial groups and is much lower in black populations, and among Eastern and South-eastern Asians [5]. In this report, we present a brief review and rare case of an 8-year-old elementary schoolboy, diagnosed with Ewing's sarcoma of the proximal left humerus.

Case report

The patient was an 8-year-old elementary schoolboy who had been previously diagnosed with ES. He came with chief complaints of left shoulder pain during daily activity and swelling in the past two weeks before the presentation (Fig.1). The complaints appeared after two months of resting and discontinuation of chemotherapy schedules. His family had also been reported to have ignored the surgery treatment proposed by the doctor from another hospital. The pain mainly occurred during activity and occasionally at night, which were somewhat alleviated by analgesics such as ibuprofen and acetaminophen. On physical examination, we found a hard and tender mass on the upper one-third of the left humerus, which was covered by healthy appearing skin. Patient's range of movement was limited.



Fig 1: Physical Examination.

On plain radiograph of the shoulder revealed (Fig.2) permeative lytic with a sclerotic mixture lesion with indistinct border and broad transition zone, which was seen from proximal metaphysis to the distal diaphysis of the left humerus. The extension of the lesion to the epiphyseal plate was difficult to evaluate. Aggressive periosteal reactions (Sunburst and Codman triangle) were seen on proximal metaphysis and distal diaphysis of the humerus. Prominent soft tissue swelling with osteoid matrix ossification was seen at the proximal to the mid humerus region. These findings suggested the impression of malignant bone lesion on the left humerus, indicating an Ewing's sarcoma, with the different diagnosis of osteosarcoma.



Fig 2: Radiography of Left Shoulder (A) Antero-posterior View; (B) Lateral View.

After gaining informed consent from his parents, we conducted a confirmatory biopsy of the lesion. Microscopic

pathological examination revealed a malignant cellular tumor with foci of necrosis and infiltration of subarticular marrow spaces. Tumoral cells had uniformly round nuclei, indistinct nucleoli in some of them, and high nucleocytoplasmic ratio. Scattered mitosis and foci with rosette formation could be seen. Histologic features were those of a malignant small-round-blue-cell neoplasm (Fig.3). Immunohistochemical staining was positive for Vimentin, CD 99, and Synaptophysin, but negative for Ck, S100 protein, Desmin, and CD45 (Fig.4). The histopathologic findings were consistent with Ewing's sarcoma. We subsequently demanded the informed consent for the chemotherapy combined with surgical intervention and reconstruction using a prosthetic replacement procedure. Unfortunately, his family rejected the suggestion and chose only symptomatic treatment instead.

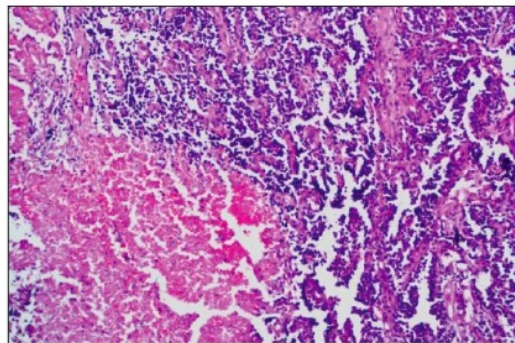


Fig 3: Photomicrograph of a Proximal Humerus Tumor (H & E, 40x)

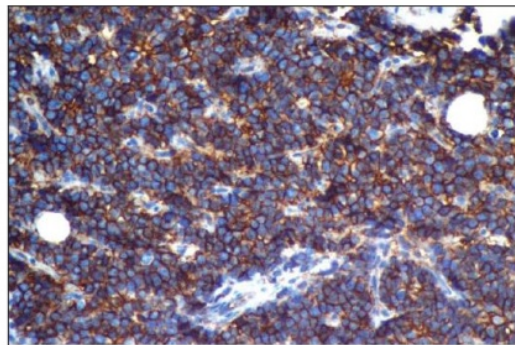


Fig 4: Immunohistochemical Staining with Positive CD99 Membrane (H & E, 40x).

Discussion

Among all childhood malignancies, the most common malignant bone tumors in children are Ewing's sarcoma (2%-3%) and osteosarcoma (3.5%). The male gender is slightly more prone to the incidence. The clinical manifestation is non-specific, with local pain being the most common symptom by far. The pain is progressively worsening with a low chance of remission. Swelling and mass, especially when the tumor is located in extremities, may be seen [6]. Ewing's sarcoma typically occurs in the extremities, specifically in long proximal bones. Primary lesions are more commonly seen in the diaphysis of the femur, tibia, and humerus [7]. The etiology of ES is still unclear. A study from Taiwan by Huang *et al.* reported that there were up to 85% of patients with ES have the chromosomal translocation of t(11;22)(q24;q12) [8]. The most alike differential diagnosis of ES is osteosarcoma (OS), which is a metaphyseal malignant bone tumor

composed of mesenchymal cells producing osteoid and immature bone. Osteosarcoma is rarely rose in the soft tissues. There are two varieties OS including the high grade and low grade [9]. The OS is more common in adolescents younger than 20 years; whereas ES is more prevalent in children younger than 10 years [10]. The signs and symptoms of OS are local pain, followed by localized swelling and limitation of movement [11].

Tow *et al.* reported an osteomyelitis case in 24 years old man who presented to the Singapore General Hospital with a one-week history of right pain and fever. Plain radiograph, magnetic resonance imaging (MRI), and bone scan showed a consistent finding of an active localized lesion of the bone, with histological finding from open biopsy revealed only chronic inflammation and no malignancy. The patient was treated for six weeks with antibiotics (ampicillin, cloxacillin) and analgesics. The patient responded well and had a complete recovery of the symptoms. Five months later, the patient had a recurrence of symptoms. The second biopsy showed a suggestive finding of ES [12].

It is essential to do a follow-up investigation of diagnosis and consider other etiologies for our patient's presenting symptoms during the initial workup. As we know, the classic radiographic appearance of ES with "Onion-skinning" periosteal reaction can also be seen in osteomyelitis [13]. Moreover, the presence of ES may indicate an elevated levels of arachidonic acid metabolite and prostaglandins. Therefore, the use of non-steroidal anti-inflammatory agents and COX-2 inhibitors have been shown to inhibit the growth of tumors in animal studies. Tsutsumi *et al.* stated that some tumors have respond to antibiotics and anti-inflammatory drugs [14].

There are some indicative laboratory examinations for ES, such as complete blood count (CBC), lactate dehydrogenase (LDH), and alkaline phosphatase test (ALP). Nonspecific inflammation process marked as an elevated erythrocyte sedimentation rate (ESR), leukocytosis, and elevated LDH may be found [15]. The definitive diagnostic procedure for ES is the incisional biopsy, additionally with cytogenic immunohistochemical to differentiate the ES with other tumors [15].

Enneking *et al.* invented the staging system for benign and malignant musculoskeletal tumors to support decision making in treatment choice. The system is based on the histological grade of the tumor, the local extent, and the presence or absence of metastasis. High-grade lesions, such as ES, are designed as stage II tumors, which can be subdivided according to the extent of local growth. While stage IIA lesions are contained within well-defined anatomical compartments, stage IIB lesions extend beyond their compartment of origin. Stage III includes any lesions that have metastasized, regardless of the size or grade of the primary tumor. Almost all ES fall into stages IIB or III [16]. The possibility of primary metastasis is pulmonary organs. Rastogi *et al.* reported that 14 out of 57 cases of ES had pulmonary metastases before surgical treatment [17].

The treatment for ES consists of a combination of chemotherapy and surgery. The type of surgical procedure depends on the tumor stage, response to chemotherapy, patient's age, general condition, and life expectancy. Current anti-cancer drugs which are proven to be effective against ES are doxorubicin (DXR), cyclophosphamide (CPA), vincristine (VCR), actinomycin-D (ACT), ifosfamide (IFM), and etoposide (VP16) [18]. The current standard treatment schedules for resectable ES begin with neoadjuvant chemotherapy, followed by limb salvage procedure and

postoperative adjuvant chemotherapy. Although amputation had been the only surgical method for several decades; the limb salvage procedure, which includes local resection and reconstruction, are currently performed in almost all the cases of ES. Limb salvage procedures can be performed without compromising survival rates [19].

In orthopedic oncology principles, surgical margin can be described by one of four terms: intralesional, marginal, wide, or radical. An intralesional margin is one in which the plane of surgical dissection is within the tumor, which is often called "debulking", because it leaves gross residual tumor behind. A marginal margin is achieved when the closest plane of dissection passes through the pseudocapsule of the tumor. The pseudocapsule, however, often contains microscopic tumor foci. Marginal resection often leads to local recurrence if the remaining tumor cells do not respond to adjuvant chemotherapy or radiation therapy. Wide margins are the goal for most procedures, especially with high-grade malignancies such as ES. Radical margins are achieved when all compartments that contain tumor is removed en bloc [20].

After resection of ES, large bone defects should be reconstructed to restore the function of the affected limbs. The main options for reconstruction include autogenous bone grafts and endoprostheses. Late complications of this reconstruction are the loosening, infection and fracture of the graft or prosthetic after replacement [20]. Prognosis of ES is highly dependent on clinically evident metastatic disease, which may be preventable with early detection and treatment with aggressive local disease control and systemic multidrug chemotherapy [13]. Because of the small number of ES cases, the statistical power is limited. Nevertheless, we believed that innovative gene therapies, targeted therapies, and immunotherapies may improve the survival rate of patients with ES. However, based upon the plain radiography and biopsy results at presentation, the prognosis of our case is expected unfavorable.

Conclusion

Ewing's sarcoma is a rare bone tumor that typically occurs in the extremities. It is a highly aggressive tumor that metastasizes primarily to the lungs and other organs. Chemotherapy development and surgery improvement have allowed a revised treatment of ES in recent years. Advances in treatments which are based on immunotherapies and targeted chemotherapy may improve the survival rate of patients with ES.

Conflict of Interest

The authors reported no potential conflict of interest relevant to this article.

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