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Case Report

Case Report – Ewing Sarcoma: clinical and histopathological aspects

Relato de caso - Sarcoma de Ewing: aspectos clínicos e histopatológicos

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ABSTRACT

Ewing sarcoma is the second most common primary bone neoplasm in childhood, primarily affecting bones and soft tissues. The aim of this study is to report a typical case of this neoplasm, highlighting its clinical and pathological features. We present the case of a 9-year-old female patient with a history of chronic pain in the right lower limb, gradually progressing over more than 10 months. The patient was diagnosed with Ewing sarcoma and initiated chemotherapy, followed by a limb-sparing surgical procedure. At the end of the treatment protocol, she presented only postoperative changes. Follow-up was carried out regularly, and a recurrence was diagnosed one year and two months later. The patient was re-evaluated by the surgical team and underwent amputation of the right lower limb. She is currently undergoing adjuvant chemotherapy. This case illustrates the importance of early diagnosis and continuous follow-up in pediatric bone neoplasms.

RESUMO

O sarcoma de Ewing é a segunda neoplasia óssea primária mais comum na infância, acometendo principalmente os ossos e as partes moles. O objetivo deste trabalho é relatar um caso típico dessa neoplasia, evidenciando suas características clínicas e patológicas. Trata-se do caso de uma paciente do sexo feminino, de 9 anos de idade, com histórico de dor crônica em membro inferior direito, com evolução gradual há mais de 10 meses. A paciente foi diagnosticada com sarcoma de Ewing e iniciou tratamento quimioterápico, seguido de cirurgia conservadora. Ao término do protocolo, apresentava apenas alterações decorrentes do status pós-cirúrgico. O acompanhamento ocorreu de forma regular, com diagnóstico de recidiva após um ano e dois meses. Foi reavaliada pela equipe cirúrgica e submetida à amputação do membro inferior direito. Atualmente, segue em tratamento quimioterápico adjuvante. O caso ilustra a importância do diagnóstico precoce e do acompanhamento contínuo em neoplasias ósseas pediátricas.

INTRODUCTION

Ewing sarcoma (ES) is a poorly differentiated malignant neoplasm that develops in the bones or soft tissues. Histologically, the classic form is characterized by small, round, blue cells with scant cytoplasm, which may contain glycogen, without evidence of histological differentiation[1]. In cases originating in bone, it begins in the medullary cavity, later invading the cortex, periosteum, and soft tissues, resulting in areas of hemorrhage and necrosis[2].

It is the second most common primary bone neoplasm in childhood, surpassed only by osteosarcoma[2]. It occurs more frequently in children and young adults, with an average age between 10 and 15 years and a slight predominance in males. Clinically, patients present with pain and local swelling associated with reduced joint mobility, which may progress to persistent pain, poorly relieved, and difficulty walking[1,3].

ES most commonly affects long bones, such as the femur and humerus, but it may affect other bones, such as the pelvis and ribs[4]. In some cases, the neoplasm may occur in its extraosseous form, with a predilection for the trunk, especially the retroperitoneal region[5]. Dissemination occurs predominantly via the hematogenous route, resulting in metastases mainly in the lungs, other bones, and bone marrow[4,5].

One of its main molecular characteristics is the *EWS-FLI1* gene fusion. This genetic alteration is highly specific, as it is almost exclusive to ES, and it is present in approximately 95% of cases, also providing high sensitivity[3]. Several immunohistochemical markers are used in the diagnosis of ES, the most important being CD56, CD99, NKX2.2, and FLI1[6].

Most patients present with localized disease at the time of diagnosis, with a five-year survival rate of approximately 80%. About 25% of patients have metastases at diagnosis[5,7], and these patients tend to have a poorer prognosis[3,6]. This direct relationship between localized disease and survival demonstrates that one of the main factors influencing prognosis is early diagnosis.

The present study aims to report a classic case of this neoplasm, serving as a reference for the early identification of Ewing sarcoma. It was prepared in accordance with current ethical principles, with approval from the Research Ethics Committee of Faculdade Pequeno Príncipe (CAAE 82395424.6.0000.5580) and the obtaining of informed consent from the patient's legal guardians for the disclosure of information, ensuring respect for privacy and anonymity.

CASE REPORT

A 9-year-old female patient presented to the emergency department of a pediatric hospital with complaints of pain in her right leg. The pain was articular in nature, with onset approximately ten months earlier, associated with significant weight loss (11 kg) and fever. Initially, it occurred sporadically, with greater intensity at night, without limitation of walking or daily activities, and improved after the use of tramadol. Prior to the pain, the patient showed normal development for her age, with no personal or family history of genetic or oncological diseases. She progressed with local swelling and limping, and was referred for clinical follow-up, with an initial suspicion of juvenile rheumatoid arthritis. She was also assessed by an orthopedic specialist, who recommended Magnetic Resonance Imaging (MRI) of the affected limb to rule out a bone neoplasm. MRI revealed an expansive bone lesion, with severity suggestive of osteosarcoma.

The family moved to another state seeking specialized medical care. At this point, the patient presented with swelling, pain, and limited movement in the right knee. Given the clinical and radiological suspicion of a neoplastic process, she was referred for evaluation in the pediatric Oncology and Orthopedics depart-

ments, where additional tests were requested. A new MRI confirmed an aggressive bone lesion, centered on the medial surface of the distal femoral diaphysis, extending to the epiphysis and involving the deep femoral vascular bundle, measuring 24.7 cm in length and 6.5 × 7.8 cm anteroposterior by transverse in the axial plane. The anatomopathological examination revealed a poorly differentiated malignant neoplasm composed of small, round, blue cells (**Figure 1**).

To better assess the histogenesis of the neoplasm, an immunohistochemical study was performed, showing positive staining for CD99, FLI-1, and NKX2.2 (**Figure 2**).

A genetic panel for pediatric neoplasms was also performed, showing the presence of the *EWSR1-FLI1* fusion, confirming the diagnosis of ES. During the patient's evaluation, staging tests were conducted. Chest computed tomography (CT) revealed no secondary thoracic implants. The bone marrow aspirate showed no neoplastic cells, and the echocardiogram also presented no abnormalities. The patient began treatment following the "Ewing Family" protocol used by the hospital. This protocol includes induction chemotherapy consisting of three cycles of vincristine, doxorubicin, and cyclophosphamide, alternated with ifosfamide and etoposide.

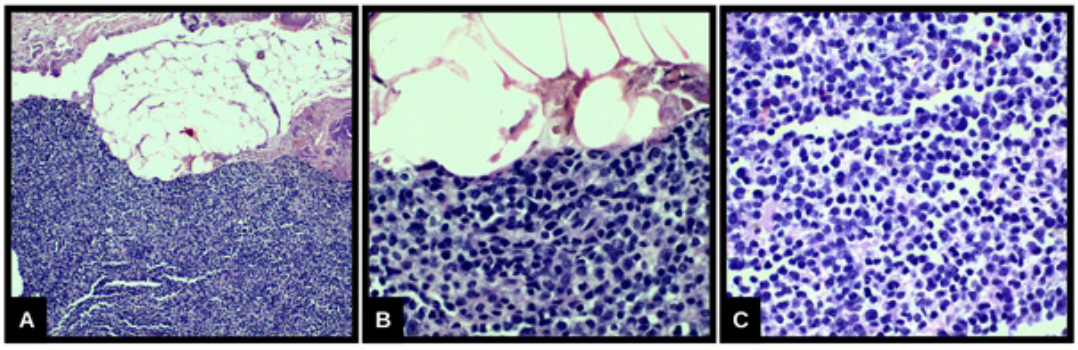

Figure 1. Poorly differentiated malignant neoplasm. A and B – Note infiltration of adipose tissue (Light microscopy, Hematoxylin and eosin, 10x and 40x objective lenses); C – The tumor is composed of small, round, blue cells (Light microscopy, Hematoxylin and eosin, 40x objective lens).

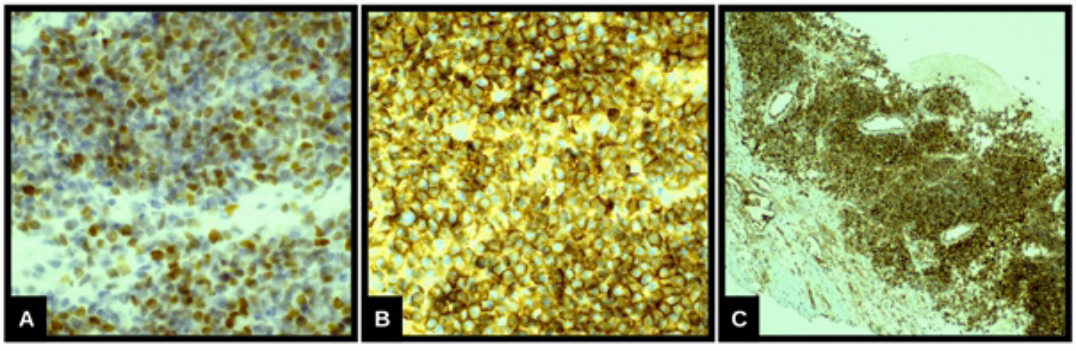

Figure 2. Antibodies used to determine tumor histogenesis. A – Nuclear positivity for CD99 (Light microscopy, Immunohistochemistry, 40x objective lens); B – Membranous positivity for FLI-1 (Light microscopy, Immunohistochemistry, 40x objective lens); C – Strong and diffuse positivity for NKX2.2 (Light microscopy, Immunohistochemistry, 4x objective lens).

After neoadjuvant chemotherapy, new tests were performed to assess treatment response. MRI of the right lower limb showed signs of partial regression of the neoplasm. Chest CT showed no signs of metastasis. Local surgical control was performed using the frozen bone or frozen autograft technique, which consists of tumor excision followed by preparation for internal fixation. The excised bone segment is frozen in liquid nitrogen to destroy neoplastic cells, then thawed at room temperature and in distilled water before reimplantation. Preoperative evaluation confirmed the presence of residual malignant neoplasm. This surgical technique does not allow complete anatomopathological assessment, making it impossible to confirm histological status of surgical margins.

However, following oncological principles and international recommendations, margins were planned widely in advance based on preoperative imaging. In addition, liquid nitrogen freezing eliminates residual tumor cells, making the bone reimplantation safe. After surgery, another chemotherapy cycle was administered according to the previously described protocol.

At the end of treatment, MRI of the right lower limb showed marrow signal alteration and changes in the solid component on the medial surface of the distal femoral diaphysis, consistent with postoperative status, which remained unchanged on a subsequent MRI performed for comparison. The patient continued follow-up with the Oncology and Orthopedics departments.

After one year and two months, the patient presented to the emergency department with recurrent fever and swelling of the right lower limb, with local warmth and pain on flexion and extension. She was hospitalized for further investigation. A new MRI revealed an expansile lesion with poorly defined margins in the posterior region of the distal femur, measuring approximately 7.0 cm in length and 5.0 × 5.8 cm (anteroposterior × transverse) in the axial plane. CT showed a small pulmonary nodule in the left lower lobe. A biopsy of the lower limb lesion was requested, confirming a poorly differentiated malignant neoplasm composed of small, round, blue cells with areas of necrosis, similar to the previous diagnosis. Immunohistochemistry, with positivity for CD99, NKX2.2, FLI-1, and CD56, confirmed recurrence of ES. The patient was referred for another surgery, with amputation of the right lower limb and chemotherapy, and is currently under follow-up.

DISCUSSION

Childhood neoplasms are among the leading causes of death in this age group in several countries[8]. Mortality rates are significantly higher when diagnoses are delayed and neoplasms are detected at advanced stages[9,10]. ES is a rapidly progressive neoplasm with high metastatic potential, which makes early diagnosis a decisive factor for prognosis[7].

ES tends to affect children between 10 and 15 years of age, predominantly males and those of Caucasian descent[2,5,9]. The patient in this report was diagnosed at 9 years of age, a range close to the expected epidemiological peak. Retrospectively, the clinical presentation was typical, with bone pain that worsened at night, local swelling, and decreased joint mobility. However, because the symptoms are quite nonspecific when presented in isolation, they hinder clinical diagnosis.

Primary bone tumors are among the pediatric neoplasms with the most delayed diagnosis[10]. This is associated with several factors, such as the short latency period and rapid growth, which means that diagnostic delays significantly reduce the chance of cure[10,11].

In addition, pediatric neoplasms may present with nonspecific clinical manifestations that

often overlap with other more prevalent diseases in this age group[9,10]. Most patients with ES and other bone neoplasms initially present with local pain, which may be mistaken for bone growth or everyday trauma[4]. In the case reported, the first clinical suspicion was juvenile idiopathic arthritis, reflecting the difficulty of establishing a diagnosis in the presence of nonspecific symptoms.

In this context, it is important that general healthcare professionals in primary care are able to recognize warning signs in complex cases and refer patients to specialists when necessary. In cases where pain persists for more than one month without improvement, further investigation should be pursued[4]. Delayed diagnosis of childhood neoplasms is associated with the need for more aggressive therapies and, consequently, increased morbidity and mortality[9].

ES is an aggressive neoplasm, and a portion of patients already present metastases at the time of diagnosis[7]. In patients with localized disease, prognosis is better, with approximately 80 percent five-year survival. On the other hand, patients with metastases at diagnosis show a significant reduction in overall survival, which varies according to the location and number of secondary implants[4,7].

The patient reported initially presented with a localized neoplasm in the distal femur and without secondary implants, which indicated a better prognosis. However, at the time of recurrence, a pulmonary nodule was observed. This case highlights how prognosis may change throughout the clinical evolution of the disease. Despite the radiological suspicion of secondary implant, the lesion was not biopsied.

The diagnosis of ES is established through a combination of radiological, anatomopathological, and molecular examinations[7]. In the patient described, MRI revealed an expansive bone lesion with severe features, which justified biopsy and detailed investigation. The differential diagnosis should include infections, such as osteomyelitis, as well as hematologic neoplasms, such as leukemias.

The neoplasm generally develops in the medullary cavity, subsequently invading the cortex and periosteum[1]. The tumor mass usually presents areas of hemorrhage and necrosis. Microscopically, ES appears as a poorly differentiated neoplasm composed of small, round, blue cells with scant cytoplasm and areas of necrosis[1,3,6].

Several immunohistochemical markers are used to support the diagnosis, among which CD56, CD99, NKX2.2, and FLI1 stand out. Their use is essential for confirming the diagnosis of ES, as well as for excluding differential diagnoses[6]. Each of these markers is associated in some way with the development of ES, and, when used together, they are highly specific for this neoplasm[7].

CD56 is expressed in a variety of pediatric tumors, and studies have shown that the expression of this marker is associated with poorer prognosis[6,12]. CD99 is a highly sensitive marker, being present in 95 percent of ES cases[4]. However, this marker is positive in several mesenchymal tumors, which results in low specificity and requires association with other markers to confirm ES[6].

NKX2.2 protein expression shows good sensitivity and moderate specificity, being related to neuroendocrine differentiation and acting as a transcriptional target of the *EWSR1-FLI1* fusion[6,7]. Its specificity increases significantly when used together with CD99[7].

Immunopositivity for FLI1 occurs in patients who present the *EWSR1-FLI1* gene fusion[6]. This marker is more specific than CD99, although it can also be present in some leukemias and lymphomas, which limits its specificity[4].

The translocation between chromosomes 11 and 22 is the most important feature of this tumor, generating the *EWSR1-FLI1* or *EWS-ERG* fusion gene[13]. This fusion produces a chimeric protein that induces the transcription of genes that contribute to tumor development by interfering with cell proliferation, differentiation,

cell cycle, and apoptosis[3,4]. Approximately 90 percent of patients with ES, including the patient in this report, present the *EWSR1-FLI1* fusion gene, which makes its detection an important diagnostic tool[2,4,6].

Currently, treatment is performed with nonspecific cytotoxic drugs. Before the development of current protocols, mortality related to ES was extremely high. Overall survival has improved significantly after their implementation[5]. Recent research aims to develop targeted drugs for the markers present in ES. However, drugs that directly interfere with the chimeric protein have shown limited efficacy[14]. Other ongoing research targets drugs that act on the tumor microenvironment and on transcriptional targets of *EWSR1-FLI1*, such as inhibitors of polymerase 1 (PARP1), IGF-1 receptor, and CD99[3,15]. Despite advanced knowledge of molecular targets, there are still significant challenges in translating them into effective therapies in the clinical setting.

When possible, more conservative strategies are preferred to treat the neoplasm while preserving the patient's quality of life. In the patient's initial therapeutic approach, instead of amputation, a more conservative technique was chosen to preserve the affected limb. The use of the frozen bone or frozen autograft technique as a surgical treatment represents a strategy aimed at maintaining bone structure, with fewer complications and reduced morbidity. Functional and therapeutic outcomes are similar, but with shorter operative time and better implant adaptation[16]. In the reported case, tumor recurrence required amputation of the limb.

In the past, local control of Ewing sarcoma was predominantly achieved through amputations. However, with advances in surgical and chemotherapeutic techniques, limb-preserving strategies have become a priority. Surgical treatment remains the main method of local control, although there is still no consensus on the ideal bone reconstruction method in pediatric patients[17].

The choice of technique is multifactorial and considers factors such as age, expected growth, response to chemotherapy, presence of metastases, and availability of resources[18]. Reconstructions may be biological (using autologous or allogeneic grafts) or prosthetic[19]. In the reported case, because the patient was a child, the use of a prosthesis could result in early failure due to bone growth, and allogeneic grafts were not available due to the absence of a pediatric bone bank.

Given this scenario, the frozen autograft technique was selected. This method has been described in the literature for the management of bone neoplasms and enables limb preservation with good potential for osteoinduction, osteoconduction, and anatomical integration[16,17,20]. Although this technique is not directly cited in guidelines from cooperative groups (SIOP[21], SOBOPE[2], SLAOP[2]), these guidelines recommend viable reconstructive surgery, leaving the choice of technique to specialized and individualized judgment. It is worth noting that recent studies show recurrence and overall survival rates similar to other reconstruction modalities[17,22].

A known limitation of this method is the impossibility of sending the entire piece for anatomopathological analysis, restricting evaluation to fragments[16,20]. However, liquid nitrogen freezing promotes complete destruction of residual neoplastic cells and is considered safe when performed with wide preplanned margins.

Recurrence of Ewing sarcoma is associated with multiple factors, including tumor size, location, histological response to chemotherapy, surgical margin status, and time to recurrence. Large tumors located in central bones and with less than 90 percent necrosis after chemotherapy have a higher risk of local and systemic recurrence[14]. Furthermore, early recurrence—within two years of diagnosis—usually indicates more aggressive biological behavior and poorer prognosis[5].

This typical presentation of ES allows the assessment of several issues related to follow-up and therapeutic strategy. For early diagnosis to be achieved, it is essential that both parents and healthcare professionals are attentive to warning signs that justify further investigation in this age group. The aim of reporting this case is to enable non-specialist physicians to recognize patients who require specialized evaluation, ensuring early diagnosis and appropriate treatment.

AUTHOR CONTRIBUTIONS

KKK, SHM, and EMC contributed to the conception and design of the study, data analysis, and manuscript drafting. KKK, SHM, and EMC were responsible for data collection and critical review of the manuscript. APP and DPS performed the final review of the text. All authors read and approved the final version of the manuscript and agree to be responsible for its content.

CONFLICT OF INTEREST

We wish to confirm that there are no known conflicts of interest associated with this publication and that no significant financial support has influenced its results.

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DECLARATION REGARDING THE USE OF GENERATIVE AI

The authors declare that they used the generative artificial intelligence tool ChatGPT to assist with language revision. The editorial board made the decision to utilize ChatGPT, an AI language model developed by OpenAI, for the translation of this manuscript from the original language, Portuguese, to English.

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