



Ewing Sarcoma in the Sciatic Nerve: Case Report

Sarcoma de Ewing no Nervo Ciático: Relato de Caso

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Arq Bras Neurocir 2023;42(2):e181–e185.

Abstract

Ewing sarcoma (ES) is a malignant neoplasm that affects bones and soft tissues, usually in young patients. Currently, ES is grouped with other tumors that share the same histological and genotypic characteristics, forming the Ewing Sarcoma Family of Tumors (ESFT), which includes ES of bone, extraosseous ES (peripheral neuroepithelioma), Askin tumor, and peripheral primitive neuroectodermal tumor (PNET). Its origin in peripheral nerves is extremely rare, making its diagnosis and treatment very challenging. We describe a case of a 27-year-old male with extraosseous ES originating in the sciatic nerve, which was surgically removed, and discuss the difficulties encountered in the management of this patient.

Keywords

- ▶ Ewing sarcoma
- ▶ peripheral nerves
- ▶ primitive neuroectodermal tumor

Resumo

O sarcoma de Ewing (SE) é uma neoplasia maligna que acomete ossos e partes moles, geralmente em pacientes jovens. Atualmente, o SE é agrupado com outros tumores que compartilham as mesmas características histológicas e genotípicas, formando os Tumores da Família do Sarcoma de Ewing (TFSE), que incluem o SE ósseo, o SE extraósseo (neuroepitelioma periférico), o tumor de Askin, e o tumor neuroectodérmico primitivo (TNEP) periférico. Sua origem em nervos periféricos é extremamente rara, o que torna o seu diagnóstico e tratamento um grande desafio. Descrevemos o caso de um homem de 27 anos com SE extraósseo originário no nervo ciático, que foi removido cirurgicamente, e discutimos as dificuldades encontradas no manejo desse paciente.

Palavras-chave

- ▶ sarcoma de Ewing
- ▶ nervos periféricos
- ▶ tumor neuroectodérmico primitivo

Introduction

Ewing sarcoma (ES) is an uncommon malignant neoplasm that most often affects the bones of children and adoles-

cents.¹ In ~ 25% of the cases, ES can originate in soft tissues.² Currently, these tumors are included in the Ewing Sarcoma Family of Tumors (ESFT), because they have the same histological and genotypic characteristics.³ Extraosseous ES

received

April 15, 2021

accepted

June 16, 2021

article published online

February 2, 2022

DOI <https://doi.org/>

10.1055/s-0041-1739271.

ISSN 0103-5355.

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Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

originating from peripheral nerves is very rare. We present a case of extraskelatal ES originating in a young patient's sciatic nerve, and discuss the great challenge of treating patients with this pathology.

Case Report

A 27-year-old, Caucasian, male patient presented with complaints of progressive loss of strength in the left foot with 13 months of evolution associated with pain in the back of the left thigh with proximal and distal irradiation. Upon examination, the patient was in good general condition, with café-au-lait patches on the abdominal wall, without other stigmata of type-1 neurofibromatosis. He had a palpable mass between the middle and lower thirds of the left posterior thigh, of ~ 5 cm, mobile, non-pulsatile, painful, and with a positive Tinel sign. Upon auscultation, no murmurs were perceived. The neurological examination showed grade-0 strength for hallux extension and dorsiflexion, and grade-1 strength for left foot eversion, and tactile and painful hypoesthesia on the side of the left leg and foot. An MRI scan identified an oval, circumscribed tumor in the left sciatic nerve, without affecting the neighboring planes, without signs of edema surrounding it, with annular uptake of contrast suggestive of schwannoma/neurofibroma (►Fig. 1). An electroneuromyography exam identified axonal involvement of the left sciatic/common fibular nerve, with signs of denervation in muscles innervated by the left fibular nerve. Surgical treatment was applied, with access to the back of the left thigh to expose the sciatic nerve and the origin of the left tibial and

common fibular nerves. A tumor of ~ 7 cm in length and 3.2 cm in its largest diameter was identified, located in the final and lateral portions of the sciatic nerve and in the origin of the common fibular nerve (►Fig. 2). Circumferential dissection was performed, and no adherence to neighboring tissues was observed. The tumor was easily detached from the tibial nerve. The fascicle where the tumor originated was identified in the final portion of the sciatic nerve. Electrical stimulation showed no response. The tumor was resected en bloc, sparing a fascicle of the common fibular nerve. The sectioned fascicle was reconstructed with two 8-cm sural nerve cables each. A pathology examination described a malignant neoplasm of small cells of high cellularity and with areas of necrosis. The immunohistochemical study was negative for antibodies CKAE1/AE3, S100, actin, desmin, CK7, synaptophysin and positive for CD 99, CD 56, vimentin, Bcl-2, and rarely positive in neoplastic cells for EMA. A total of 70% of the neoplastic cells were positive for Ki67. (►Fig. 3). These characteristics were compatible with the diagnosis of peripheral primitive neuroectodermal tumor (PNET)/Ewing sarcoma. Clinical staging was performed with chest tomography, whole-body scintigraphy and bone marrow biopsy, without evidence of metastatic tumor. Chemotherapy started with vincristine, doxorubicin, and cyclophosphamide (VDC) alternated with ifosfamide and etoposide (IE) every two weeks (the VDC-IE combination) for a year of treatment, complemented with local radiotherapy. The treatment was well tolerated by the patient, who evolved with improved sensitivity in the left leg and foot, improved strength in dorsiflexion of the foot (M3) and non-functional improvement in hallux extension and eversion of the foot (M1). The

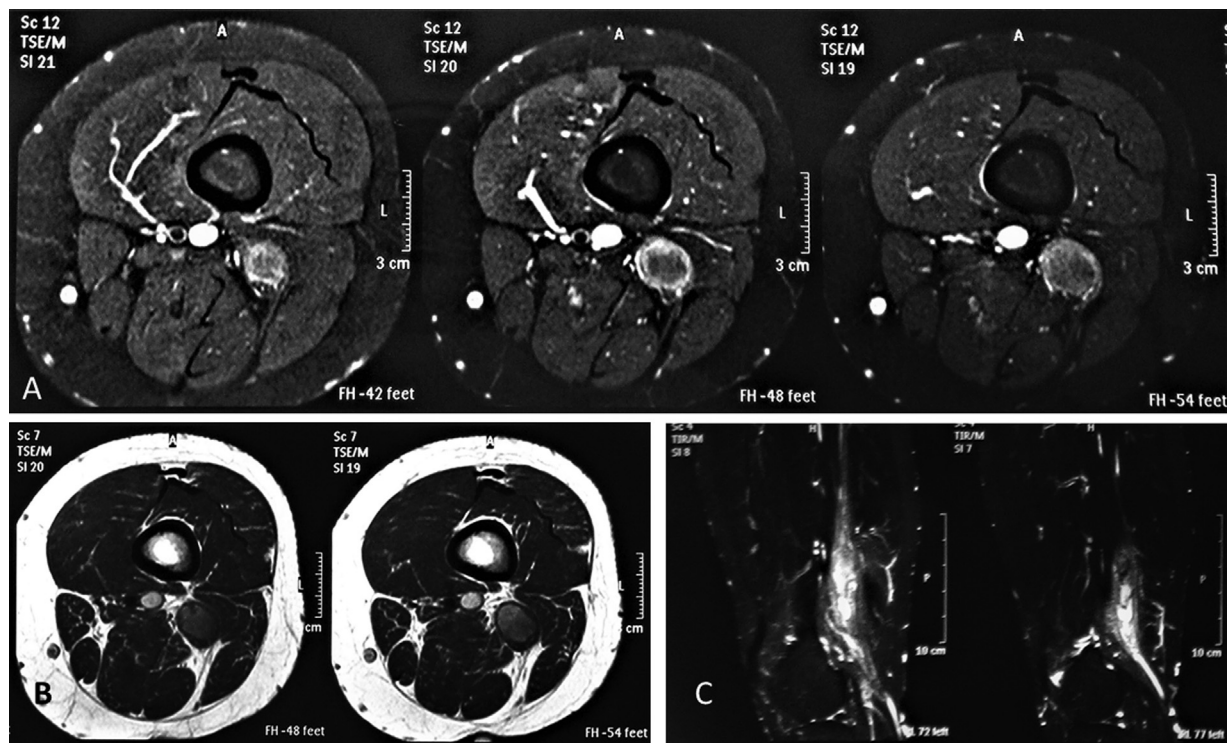


Fig. 1 (A) T1-weighted magnetic resonance imaging (MRI) in axial sections showing uptake of the contrast, more intense at the periphery. (B) T1-weighted MRI in axial sections showing regular lesion of well-defined limits without invasion of neighboring planes and without surrounding edema. (C) T2-weighted short tau inversion recovery (STIR) MRI in sagittal sections showing sciatic nerve damage in the topography of its bifurcation.

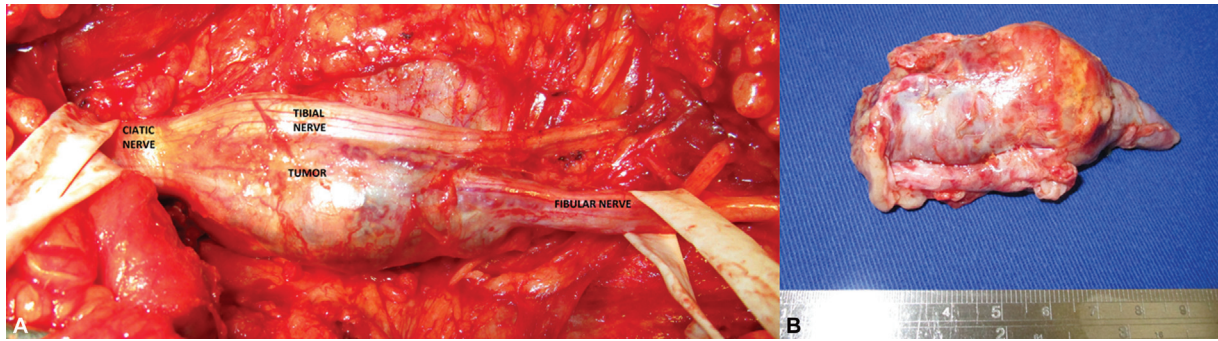


Fig. 2 (A) Photograph of the surgical field showing a tumor on the left sciatic nerve, affecting its circumscribed fibular portion, with no signs of invasion of neighboring tissues. (B) Photograph of the 7-cm long surgical specimen.

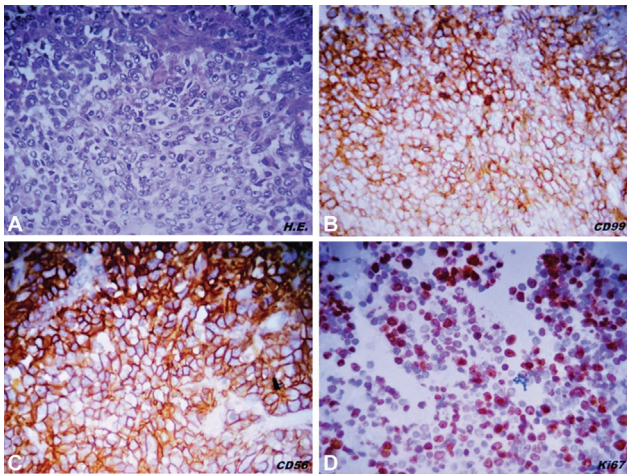


Fig. 3 (A) Slide stained with hematoxylin and eosin showing a small, blue, regular cell tumor with large nuclei and fine chromatin; magnification: 20X. (B) CD99 positivity on immunohistochemistry; magnification: 20X. (C) Positivity for CD56 on immunohistochemistry; magnification: 20X. (D) Positivity for Ki67 in 70% of tumor cells; magnification: 20X

signs of neurological recovery started with 10 months of the surgery, and progressed until the 14th postoperative month, after which it stopped, despite the physical therapy treatment for 24 months after the surgery. In the first postoperative year, the patient underwent local radiological control with MRI scans every 3 months and chest tomography every 6 months;

in the second postoperative year, the patient underwent local radiological control with MRI scans every 6 months. The last local control with MRI was performed at the 28th postoperative month, without evidence of local recurrence (► Fig. 4). The patient is still being followed-up by oncology.

Discussion

Ewing sarcoma (ES) is a rare malignancy that affects bones and soft tissues. Its incidence was of 2.93 per 1 million inhabitants in the United States between 1973 and 2004.² Despite this, it is the second most common malignant bone tumor in children and adolescents. The peak incidence occurs at 10 and 20 years of age, being uncommon after 30 years of age. Ewing sarcoma has a predilection for the male sex (male/female ratio: 1.3–1.5:1), it is more frequent in Caucasians than in Asians and Africans or African-Americans.⁴ Currently, ES is grouped with other tumors that share the same histological and genotypic characteristics, forming ESFT, which includes ES of bone, extraosseous ES (peripheral neuroepithelioma), Askin tumor, and peripheral PNET.⁵ From the histological point of view, the ESFT presents as small, round, blue cell tumors when stained with hematoxylin and eosin (H&E), homogeneous, containing varying amounts of necrosis. Additional findings of rosettes and pseudorosettes, indicating neuronal differentiation, may also be observed in cases of PNET.⁶ Another characteristic common to ESFT is the t(11; 22)(q24; q12) translocation

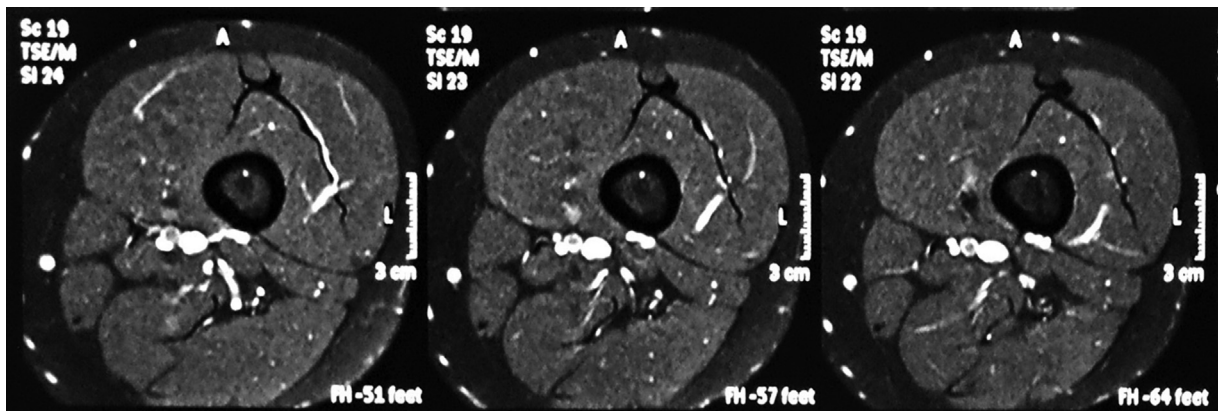


Fig. 4 T1-weighted contrast-enhanced MRI 28 months after the surgical treatment, with no signs of local recurrence.

that produces a chimeric gene called *EWSR1-FLI1*, which occurs in ~ 85% of tumors. Another fusion, which occurs in 10% of cases, is the result of translocation t (21:22) (q22; q12), which generates the *EWSR1-ERG* gene. These fusions encode chimeric proteins that function as aberrant oncogenic factors. On immunohistochemistry, about 90% of ESFT cases are positive for CD99, a membrane glycoprotein product of the *MIC2* gene.⁵⁻⁷ There are hypotheses about the origin of these tumors, among them: the theory of parental mesenchymal stem cells, and that of an origin in a primitive nerve cell or in the postganglionic cholinergic neurons of the parasympathetic system; however, the true progenitor cell of these tumors remains unknown.^{1,3,7}

About 25% of cases of ESFT are in soft tissues, affecting patients between 10 and 30 years of age, with a peak incidence at 20 years of age. The most frequent sites include the chest wall, the paravertebral musculature, the lower extremities, and the retroperitoneal space.⁴ Head and neck involvement is uncommon.⁸ There are reports of renal⁹ and pancreatic ES,¹⁰ and cases of ESFT originating in nerves are very rare. It is interesting to note that probably the first report of ESFT was made by Stout et al. in 1918, who described a case of tumor originating in the ulnar nerve, composed of round and undifferentiated cells that exhibited the formation of rosettes, and that the concept of neuroepithelioma was later proposed.¹¹ Reports of other cases of ESFT originating in the nerves are scarce. Nesbitt and Vidone¹² reported a case of PNET of the sciatic nerve in a 6-year-old patient; Martins et al.¹³ reported a case of PNET arising from a branch of the sciatic nerve in a 17-year-old female patient; and Akeyson et al.¹⁴ described a case of PNET originating in the median nerve of an elderly patient. They are typically fast-growing tumors, usually painful. Approximately 1/3 of the cases of extraosseous ES have distant metastases at the time of the initial diagnosis, but extraskelletal ES is considered a systemic lesion since its presentation, even without documented metastasis. The initial assessment is performed with MRI scans of the affected site followed by a biopsy of the tumor with a needle or an open procedure. Staging is performed with chest tomography and whole-body scintigraphy. The performance of bone marrow biopsy in the initial stage is controversial. Among the factors with the worst prognosis, the existence of metastasis in the initial evaluation is the most significant. Patients with a single lung metastasis have a slightly more favorable prognosis than those with metastases in other regions. Other unfavorable prognostic factors include age > 10 years, tumor larger than 8 cm or with volume > 200 mL, central lesions (in the pelvis or spine), and low response to chemotherapy.¹⁵

The treatment consists of systemic chemotherapy associated with local treatment (surgery and/or radiotherapy). The drugs proven effective for the treatment of ESFT include doxorubicin, cyclophosphamide, vincristine, actinomycin-D, ifosfamide, and etoposide. Currently, the regimen with VDC-IE is the protocol used in countries in North America and in many countries in Europe. The response to chemotherapy is an important prognostic factor. For local control, radical surgical resection is the best option. For those cases in which the lesion cannot be completely removed or in the absence of

an adequate safety margin, local radiotherapy would be indicated.^{2,4,6,11,15}

Considering the aforementioned information, the ideal case, the one with the best prognosis, is the patient with a localized tumor, who responds adequately to chemotherapy, and its complete surgical resection with a safety margin is possible. This raises many questions in relation to the case herein described. First, the initial diagnostic hypothesis of an ESFT, due to the rarity of the pathology, would have never been considered a probable option. There are no elements in the clinical history and neurological examination that can differentiate it from other more frequent peripheral nerve tumors such as schwannomas and neurofibromas. Second, the subsidiary exams did not provide elements that would suggest the diagnosis of this illness. The anatomical MRI exam was accurate in relation to the tumor topography and its limits, but insufficient to indicate the histological type and detect signs of malignancy. In a study comparing the characteristics of neurofibromas and malignant tumors of nerve sheaths on MRI, Wasa et al.¹⁶ described some aspects that could facilitate differentiation: mass dimensions, since malignant lesions tend to be larger; the perilesional enhancement; the perilesional edema zone; and the intralesional cystic lesion. The presence of two or more of these characteristics suggested a malignant tumor of the nerve sheath with a sensitivity of 61% and specificity of 90%. There are no studies comparing the aspects of nerve ESFT MRI with those of other tumors. Using the data found by Wasa et al.¹⁶ in our case, we would not find any indication of malignancy, because the tumor dimensions were not bulky, and there was no perilesional edema or intralesional cystic lesion. The observed peripheral enhancement can be found in neurofibromas and even in schwannomas.^{17,18} Nerve tractography and functional MRI can be valuable tools to differentiate between benign and malignant tumors of the peripheral nerves; however more studies are needed to elucidate this question.¹⁹⁻²¹

Another aspect to be discussed is the surgical treatment performed. Most peripheral nerve tumors are composed of benign lesions, and the incidence of malignant peripheral nerve tumors is of around 0.001%. In a brief review, Ball and Biggs²² described the steps of the surgical management of benign peripheral nerve tumors (BPNTs). Clinical history and propedeutic with appropriate electrophysiological and imaging tests are essential. Percutaneous biopsies of nerve tumors should be avoided, as there is a risk of nerve damage, of spread of tumor cells through the needle path, and of formation of scars that can hinder complete lesion resection. The general principles of BPNT surgical resection include adequate exposure of the lesion, including the healthy proximal and distal portions of the affected nerve, tumor inspection and intraneural dissection to identify and separate uninvolved fascicles, and electrical stimulation to identify functional fascicles. The treatment protocol for ESFT advises to initially perform a tumor biopsy to confirm the diagnosis, followed by neoadjuvant chemotherapy to observe the response. After these steps, local treatment with radical surgery with a safety margin and/or radiation therapy are indicated. In the case herein reported, we changed the order recommended in the treatment protocol for ESFT: the

surgical treatment preceded the other treatments, and this was due to a failure in the preoperative diagnosis. How this will affect the patients prognosis remains to be seen. Another aspect of the surgical treatment to be discussed is the reconstruction of the affected fascicles with a sural nerve graft. Had the diagnosis of ESFT been known, reconstruction with a graft at this time might have been contraindicated because there would be a need for radical resection with a safety margin, although there are no data in the literature to specifically guide this situation. On the other hand, it is interesting to observe the neurological evolution of this patient. Historically, the functional prognosis of patients with traumatic sciatic nerve injuries in the fibular portion or lesions in the common fibular nerve that require graft reconstruction is not favorable, especially in those cases in which the use of long grafts was necessary.^{23,24} Kim et al.²⁵ evaluated the result of the surgical treatment of traumatic fibular nerve injuries and observed that, in those in which reconstruction with a graft larger than 6 cm was necessary, a good functional result occurred in only 44% of cases. In the case herein reported, in addition to the use of grafts for reconstruction, there was a need for local control with radiotherapy, as tumor resection was not performed with a safety margin, and exposure to prolonged chemotherapy with multiple drugs, especially vincristine, which is known to cause sensory-motor neuropathy. The effects of radiation on the peripheral nerves and the possibility of postirradiation neuropathy are well known,^{26,27} but there is insufficient data regarding the influence of radiotherapy on nerves reconstructed with a graft. Even in this context, the patient described presented some degree of neurological recovery, especially sensitivity, indicating that there is possibility of nerve regeneration. Therefore, the case herein described offers the possibility of discussing several issues regarding malignant tumors of peripheral nerves, such as the difficulty in establishing the preoperative diagnosis, the limitation of imaging tests to differentiate benign from malignant lesions, and, therefore, the adequate surgical management of these injuries.

Conflict of Interests

The authors have no conflict of interests to declare.

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