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International Journal of Surgery Case Reports

journal homepage: www.casereports.com

A peculiar case of large primary cutaneous Ewing's sarcoma of the foot: Case report and review of the literature



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ARTICLE INFO

Article history:

Received 2 April 2015

Received in revised form 13 August 2015

Accepted 14 August 2015

Available online 18 August 2015

Keywords:

Extraskeletal Ewing sarcoma

Cutaneous Ewing sarcoma

Foot sarcoma

ABSTRACT

INTRODUCTION: Primary cutaneous extraskeletal Ewing's sarcomas (ESs) are extremely rare tumors, limited to the skin and generally appear as a single small lesion, circumscribed mid-to-deep dermis or involving subcutis. Due to their rarity and morphological similarity to other cutaneous tumors, ESs are subject to being clinically and pathologically subdiagnosed.

PRESENTATION OF CASE: A 37-year-old man presented a large rapidly growing mass of the first toe measuring 9.5 × 8 cm with no radiological evidence of bone involvement. The patient underwent wide surgical tumor resection; histological, immunohistochemical and molecular evaluation confirmed the diagnosis of ESs. Postoperative examinations revealed no metastasis and after 11 months follow-up no recurrences were detected.

DISCUSSION: Current literature reports only a few isolated cases or small series. ESs are generally described as small masses with a favorable clinical behavior. Despite lower extremity is a relatively frequent site, only rare and small ESs of the foot have been reported. To our knowledge the present case is the largest ES of the foot. Despite its large size, the patient did not report any metastases confirming the hypothesis of treating superficial ES with surgery alone, thus avoiding adjuvant radiotherapy and/or chemotherapy and their related side-effects.

CONCLUSION: ESs still remain exceedingly rare tumors and they could not be taken in consideration into differential diagnosis. This case represents a peculiar example of large ES in an uncommon site as the foot successfully treated with surgery alone, and may serve as an alert for those physicians who approach such rapidly growing superficial lesions.

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1. Introduction

Extraskeletal Ewing's sarcoma family of tumors (ESFT) most frequently occur in the deep soft tissues of children and young adults, such as paraspinal muscles, chest wall, and the lower extremities [1,2]. Nevertheless, it occasionally presents in a superficial location either as a primary tumor or a metastasis from osseous or deep-seated extraskeletal ESFT [1]. Those superficially located lesions, the so-called primary cutaneous extraskeletal Ewing's sarcomas, are exceedingly rare and they are limited to the skin and generally present as a single small lesion, circumscribed mid-to-deep der-

mis or involving superficial subcutis [2]. They were first described by Angerwall and Enzinger in 1975 [3]; since then the literature reports only a few isolated cases or small series as recently investigated by Delaplace et al. with a systematic review [4].

Clinically, morphologically and genetically, extraskeletal Ewing's sarcoma (ESs) and primitive neuroectodermal tumors (PNETs) share a lot of features, supporting the hypothesis that these two neoplasms are histogenetically related and then are widely considered as part of the same family of tumors [2].

Their clinical presentation usually provides a superficial single mass of 2–3 cm, soft, mobile and sometime painful with an average evolution time of 5 months [5]. A statistically female predominance with a median age at diagnosis of 17 years has been described [4]. The diagnosis may require several ancillary techniques such as aspiration cytology, histochemical stains, immunohistochemistry, electron microscopy, cytogenetics and molecular genetics of traslocations. The histological aspect of small round cells, immuno-

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Fig. 1. Large polypoid mass of the first toe of the left foot in a 37-year-old man (size, 9.5 × 8 cm). The surface shows irregular edges, necrotic and bleeding areas with several ulcerations.

histochemically positive for CD99 in characteristic membrane pattern and the specific chromosomal translocation involving gene EWSR1 in chromosome 22q12 are essential criteria for cutaneous ESs diagnosis [5,6].

Owing to the rarity of these tumors and the relative non-specificity of their histology and immunoprofile, the diagnosis of superficial ES is difficult and numerous differential diagnoses must be considered such as Merkel cell carcinoma, cutaneous lymphomas, clear cell sarcoma, malignant primitive neuroectodermal tumor, small cell carcinoma, rhabdomyosarcoma, malignant rhabdoid tumor and poorly differentiated adnexal tumors [1,5,7]. They displayed a generally favorable clinical behavior, unlike its deep counterpart, with a 10-year probability of survival rate of 91%. This is probably attributable to their small size and possibly early detection and complete surgical removal, due to their superficial location, preventing metastatic spread in most patients [4].

The principles of treatment are currently similar to Ewing sarcoma of the bone, including wide surgical resection, being associated or not with chemotherapy and/or radiotherapy, depending on its size and location, even if a definitive conclusion on the most correct treatment modalities has not yet been elucidated due to the extreme rarity of these tumors [4,5].

2. Case presentation

We described a case of a 37-year-old Caucasian man with a large rapidly growing (3 months' duration) mass of the first toe of the left foot. He denied any history of recent trauma or infections during the medical history taking; nevertheless the lesion was initially diagnosed and treated as a viral wart by the dermatologist without resolution. Physical examination revealed a 9.5 × 8 cm polypoid, necrotic mass of the first toe, with irregular edges, ulceration and bleeding (Fig. 1). He reported ambulating limitations due to pain and bulky of the tumor. Radiological examination of the foot did not reveal any bone lesion. No regional lymph node involvement was clinically detectable and ultrasonography of the inguinal region did not detect any abnormalities. The findings of a blood test were within normal limits.

The patient underwent to wide surgical resection of the lesion with a 1.5-cm margin; intraoperative sections were forwarded to pathology and typical signs of immature neoplasm were observed. Further excision with first toe amputation (up to the base of proximal phalanx) was thus necessary to obtain free surgical margins. The post-excisional defect was closed directly without wound tension. As we preserved the weight-bearing area over the first metatarsal, after surgery he was able to walk using normal shoes. Histological examination revealed a small round blue cell tumor occupying the dermis and subcutis and composed of cohesive sheets and trabeculae of uniform, small to medium round cells containing hyperchromatic nuclei with small nucleoli and scanty pale cytoplasm with indistinct cytoplasmic borders (Figs. 2 and 3). There was prominent mitotic activity (30–35 mitoses/10HPF) and mitotic index, evaluated with Ki67 was about 80%; apoptotic cells were numerous. Vague rosetiform pattern was focally present. The tumor had a lobulated growth pattern separated by fibrovascu-

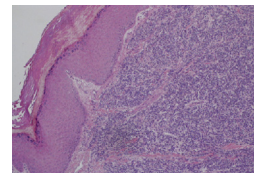


Fig. 2. Low power view (H&E, 10× magnification) of superficial Ewing's sarcoma.

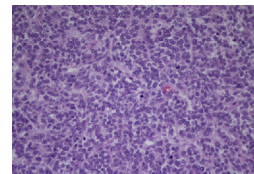


Fig. 3. High power view (H&E, 20× magnification) of extraskelatal Ewing's sarcoma characterized by small round cell tumor of striking uniformity.

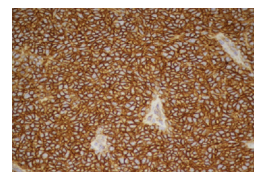


Fig. 4. Strong immunoreactivity for CD99 in a characteristic membranous pattern.

lar septa and contained extensive necrotic and hemorrhagic areas. The overlying epidermis was widely ulcerated and the deep margins were infiltrative without any bone involvement. The tumor showed only focal cytoplasmic globular periodic acid Schiff (PAS) and was immunohistochemically positive for CD99 in a characteristic membrane pattern (Fig. 4). The differential diagnosis included other small round cell tumors present in the skin such as rhabdomyosarcoma, melanoma, carcinoma including Merkel cell carcinoma, poorly differentiated synovial sarcoma and lymphoma; the distinction was possible by absence of staining for specific immunohistochemical markers such as actin, desmin, S100, HMB45, CK20, synaptophysin, chromogranin, TLE-1, Tdt, CD20 and CD3. The molecular results shows t(11;22 translocation) involving gene EWSR1.

A postoperative whole-body computed tomography (CT) scan and positron emission tomography scan using fluorodeoxyglucose (18F-FDG-PET) revealed no metastases. The patient did not receive any adjuvant chemotherapy or radiotherapy according to oncologist consultation and after 11 months of follow-up period there is no evidence of recurrence (Fig. 5). After treatment he was followed every three months through clinical examination, while magnetic resonance imaging (MRI) was performed every 6 months during the first year.

3. Discussion

ESFT are usually found in bone and deep soft tissue of young patients and they could be subdivided into osseous or extra osseous ESFT. Although extra osseous ESFT usually occur in the deep soft tissues, extremely rare superficial/dermal/cutaneous cases have been reported [1]. Due to its rarity and morphological similarity to other cutaneous tumors, cutaneous ESs are subject to being clinically and pathologically subdiagnosed [5]. Since the first report of Angerwall and Enzinger in 1975, only a few isolated cases or small series have been described in the available literature.

Delaplace et al. recently investigated with a systematic review that cutaneous ESs have usually a high 10-year probability of survival (91%) due to their superficial location, thus allowing early

Table 1

Literature review showing the largest case series or single case report with foot superficial Ewing sarcoma.

Authors	Cases	Foot lesions	Median size	Median age	Median follow-up	Median disease free time
Chow et al. [8]	14	1 (size, 2 cm)	3 cm (range, 1–12 cm)	13.8 years (range, 7–21)	64,6 months (range, 17–111)	64,6 months
Terrier-Lacombe et al. [7]	14	1 (size, 1.5 cm)	3 cm (range, 1–5 cm)	30.8 years (range, 12–77)	44.8 months (range, 11–84)	43.5 months (1 case: NA)
Ehrig et al. [10]	13	1 (size, 0.5 cm)	1.3 cm (range, 0.5–2.3 cm)	28.4 years (range, 2–67)	87,8 months (range, 18–132)	86,7 months (2 cases: NA)
Banerjee et al. [9]	8	None	3.8 cm (range, 1–10 cm)	17.1 years (range, 9–36)	36 months (range, 6–96)	36 months (1 case: NA)
Machado et al. [1]	6	1 (size, 5 cm)	4.3 cm (range, 0.5–8 cm)	44.6 years (range, 22–76)	81.6 months (range, 5–216)	81.6 months (3 cases: NA)
Hasegawa et al. [11]	5	None	2 cm (range, 0.5–7 cm)	18 years (range, 8–50)	26.6 months (range, 11–36)	26.6 months (2 cases: NA)
Shingde et al. [12]	7	1 (size, NA)	NA	31.3 years (range, 16–61)	34.7 months (range, 11–57)	34.7 months
Kourda et al. [13]	1	1 (size, 3.5 cm)	--	9 years	NA	NA

NA, not available.



Fig. 5. 11-month follow-up.

detection and removal. These tumors are generally single small masses with a median size of 2.3 cm (range 0.5–12 cm), mainly located on the lower limbs (38%), followed by upper limbs (26%), head (20%) and trunk (16%) [4], and only few studies reported the presence of multiple or large lesions [1,2,8,9]. Furthermore an accurate analysis of the literature (by using Medline, Scopus and PubMed electronic databases) displayed that despite lower extremity is a relatively frequent site of cutaneous ESs, only rare reports of primary superficial ESs of the foot have been reported, even in the largest case series. Chow et al. [8] described 14 cases with a median size of 3 cm; nevertheless only one patient had a foot lesion (size, 2 cm). Terrier-Lacombe et al. [7] reported 14 cases (median size, 3 cm) with only one foot ESs (size, 1.5 cm). Ehrig et al. [10] collected 13 cases (median size, 1.5 cm) with only one small foot lesion (size, 0.5 cm). Banerjee et al. [9] and Hasegawa et al. [11] described 8 cases and 5 cases respectively, without any foot cutaneous ESs. Shingde et al. [12] and Machado et al. [1] reported 7 cases and 6 cases respectively; every study observed one case of small tumor of the foot (size, not available and 5 cm, respectively). Kourda et al. [13] described a single case of cutaneous ES of the foot with a diameter of 3.5 cm (data summarized in Table 1).

To our knowledge the present case is the largest primary cutaneous ES of the foot. Despite its large size, the patient did not report any metastases and these findings support the data already

described in the literature. Indeed, this superficial ES displays a low rate of metastatic spread in most patients and the presence of metastases is really rare [4,5,14].

The patient was successfully treated with wide surgical removal alone, thus avoiding adjuvant radiotherapy and/or chemotherapy and their related side-effects, and he is free from disease after 11 months. Despite the short follow-up period, this confirms the hypothesis of treating primary cutaneous ESs with surgery alone and the need to reconsider its therapeutic protocol due to the extreme rarity of this tumor and the small number of available cases [4,14].

4. Conclusions

Although some cases of primary cutaneous ESs have been described, they still remain exceedingly rare tumors and they could not be taken in consideration into differential diagnosis. Despite their median size is generally small, due to their superficial location and earlier detection, some reports of large neoplasm have been reported. The present case represents a further and peculiar example of large cutaneous ES in an uncommon site as the foot and may serve as an alert for those physician who approach such rapidly growing superficial lesions. A prompt clinical, histological, immunohistochemical and cytogenetic diagnosis and a proper treatment remain fundamental for their correct management.

Conflict of interest

None.

Funding

None.

Consent

Consent obtained.

Ethical approval

None.

Author contributions

Dr. Grasseti performed the surgical procedure and participated to the study design and the writing of the manuscript.

Dr. Torresetti led the study design, the analyses of the literature and the writing of the manuscript.

Dr. Brancorsini and Dr. Rubini performed histological and immunoistochemical evaluation and participated to the study design and the writing of the manuscript.

Dr. Lazzeri participated to the study design and literature review.

Prof. Di Benedetto participated to the study design and coordination, and drafted the manuscript.

All authors read and approved the final manuscript.

Guarantor

Dr. Luca Grasseti.

Acknowledgement

We thank Dr. Angelo Paolo Dei Tos (Unit of Anatomy, Pathological Histology, Cytodiagnostic and Cytogenetics, Hospital of Treviso, Italy) for his important contribution to molecular analysis.

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