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Case Report

Cutaneous Ewing Sarcoma and Ewing Sarcoma of the Bone: Distinct Diseases?

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Abstract
Ewing sarcoma is an aggressive mesenchymal malignancy. It is the second most common bone tumor among children and adolescents and less commonly presents as a soft tissue or primary skin lesion. Cutaneous Ewing sarcoma has only been reported in case reports and case series. In this article, we describe a 12-year-old Hispanic female cured of localized, cutaneous Ewing sarcoma (pT1aN0M0) at the 40-month follow-up following surgical resection and adjuvant chemotherapy according to the COG AEWS1031 protocol for Ewing sarcoma of the bone. To our knowledge, this is the first article to provide a potential biological explanation for the differences in the prognosis of Ewing sarcoma of the bone, soft tissue, and skin.

Introduction

Ewing sarcoma (EWS) is an aggressive mesenchymal malignancy. It is the second most common bone tumor among children and adolescents and infrequently presents as soft tissue (extraskeletal EWS or EES) or subcutaneous/cutaneous EWS (scEWS) [1, 2]. scEWS has only been reported in case reports and case series. In a retrospective analysis of the Euro-Ewing99

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database in France, only 2.7% of those with EWS (24/1,005 patients) were found to have scEWS [3].

scEWS most commonly presents as a 2- to 3-cm (range 0.5–12 cm) superficial mass on the trunk or lower/upper extremities of young females (female/male ratio: 1.9), while EWS of the bone is most commonly observed in the upper extremities of males (male/female: 1.5) [2, 3]. EWS of the bone, EES, and scEWS share similar molecular and cytogenetic characteristics, including strong membranous expression of CD99 (MIC2) and the presence of a EWSR translocation involving chromosome 22 [2].

Despite similarities underlying the biology of the disease, each of the three subsets of EWS harbor distinct prognoses. EWS of the bone has the poorest prognosis, with a 5-year overall survival of 60.2% – more specifically, 78.6% among those with localized disease and 39% in those with metastases, respectively [1, 4]. 26–28% of the patients present with metastatic disease and the 5-year relapse-free survivals are 22 and 55% in those with and without metastases ($p < 0.0001$) [1, 5]. In a retrospective analysis by Applebaum et al. [6] , the 5-year overall survival of EES and EWS of the bone was 69.7 versus 62.6% ($p = 0.02$), suggesting a worse prognosis of EWS of the bone relative to EES. In contrast, scEWS has a 4- to 5-year overall survival of 91–94% and a 5-year event-free survival of 88.5%; 7.1% of the patients develop disease progression and only 3.6–9.8% either present with or develop metastatic disease, respectively [2, 3]. Thus, EWS of the bone has the worst prognosis, and patients with EES and scEWS appear to have much better outcomes.

Given the rarity of EES and scEWS, these diseases are treated similarly to EWS of the bone, with surgical resection as front-line therapy, followed by adjuvant chemotherapy with or without radiotherapy depending on the presence or absence of complete versus incomplete surgical resection. In North America, a 5-drug combination with alternating cycles of vincristine-doxorubicin-cyclophosphamide and ifosfamide-etoposide with interval compression (COG AEWS0031 protocol) is the standard of care for localized EWS, and cyclophosphamide and topotecan are used for recurrent or metastatic disease [4, 7]. Clinical trials are currently underway assessing the use of vincristine-doxorubicin-cyclophosphamide and ifosfamide-etoposide in combination with ganitumab, a monoclonal antibody directed against insulin-like growth factor 1 receptor, as a replacement for cyclophosphamide and topotecan in patients with metastatic disease. In Europe, a 4-drug combination of vincristine-ifosfamide-doxorubicin-etoposide followed by vincristine-actinomycin-ifosfamide and consolidation with vincristine-actinomycin-ifosfamide and VAC or high-dose busulfan-melphalan followed by autologous hematopoietic stem cell transplantation is used to treat metastatic disease [8].

Here, we present a case of primary scEWS that was treated according to the COG AEWS1031 protocol with an excellent prognosis at the 40-month follow-up. As these cases are rare, it is of value to share the presentation, treatment, and outcomes of scEWS with the medical community. In addition, we introduce a potential explanation for the variability in prognosis of the differing EWS subtypes based on underlying disease pathology and discuss the management of these diseases.

Case Report

A 12-year-old female of Mexican descent with a history of asthma, obesity, hypothyroidism, and fracture presented with a complaint of a flesh-colored skin lesion localized to the left mid-back. According to the patient, the lesion progressively doubled in size and developed tenderness to palpation along with a central area of erythema over 3 months (Fig. 1). On

physical examination, a 1 × 2 cm, deep, soft, tender, possibly fluctuant lesion was noted with a prominent center and minimal hyperpigmentation without induration.

The patient was empirically treated with antibiotics for a possible abscess without response to therapy. Thereafter, the lesion was fully resected and a diagnosis of primary cutaneous EWS was made by cytology, immunohistochemistry, fluorescence in situ hybridization (FISH), and cytogenetics. Histological evaluation of the lesion revealed a 1.2-cm high-grade proliferation of round-to-oval blue cells with round, irregular nuclei, fine chromatin, and occasional prominent nucleoli arranged in sheets. The lesion was found to involve the dermis and subcutaneous adipose tissue. Surgical margins were positive, and immunohistochemistry was positive for CD99 and FLI1. Stains for pan-cytokeratin, CK20, CD20, synaptophysin, chromogranin, CD3, TdT, CD34, HMB45, myogenin, desmin, WT-1, SMA, and MSA were negative, ruling out other pathologies, including Meckel cell carcinoma, melanoma, lymphoproliferative processes, rhabdomyosarcoma, neuroendocrine tumor, and neuroblastoma. EWSR1-FLI1 was detected in 88% of tumor cells by FISH and cytogenetics. Whole-body PET revealed possible metastatic disease to the left axillary lymph nodes. On further evaluation, an abscess was identified in the left axilla and was subsequently drained and treated with antibiotics. Whole-body bone scan was negative for osseous metastatic disease.

Given the patient's positive surgical margins, she underwent repeat surgical resection with wide margins. A 6-mm maximal tumor margin was obtained without evidence of lymphovascular invasion or lymphatic spread. Bilateral bone marrow aspirates and biopsies were negative for malignant disease. The patient was diagnosed with pT1aN0M0 disease and was treated with adjuvant chemotherapy according to the COG AEWS1031 protocol. She completed her therapy without significant complications and is doing well at 40 months following initial presentation.

Discussion

In this study, we describe an adolescent cured of localized, pT1aN0M0 scEWS at the 40-month follow-up. This is consistent with the good prognosis of scEWS previously described. Wide variations in the prognosis of EWS of the bone, soft tissue, and skin, however, raises the question as to whether these are distinct clinical entities that should be managed differently.

To date, differences in prognosis have been attributed to early disease detection in scEWS [2]. This likely contributes significantly as outcomes are inversely related to the depth of disease origin, with the most superficial scEWS harboring the best prognosis and less palpable, deeper EES and EWS of the bone having a latent period characterized by disease progression prior to diagnosis. However, it is also possible that these malignancies are, in fact, differing entities that harbor similar mechanisms of transformation.

While EWS-ETS family gene fusions and CD99 are commonly expressed in these diseases, the oncogenic translocations and molecular changes may arise in distinct cells of origin. Preclinical models introducing EWS-ETS family gene fusions into human fibroblasts, osteochondrogenic progenitors, rhabdomyosarcoma cell lines, and human embryonic stem cells, for instance, have been shown to transform these cells into EWS-like cells in vitro and in vivo [9–12]. Furthermore, in rhabdomyosarcoma, hedgehog signaling in endothelial progenitors leads to transformation exclusively in the head and neck (which is associated with a good prognosis) and not at other locations (associated with poorer prognoses), thus making it likely that the cell of origin differs at different sites, similar to what may be observed in EWS [13]. However, given the rarity of EES and scEWSs, no study has yet investigated the stem cell origin in

these diseases. In addition, EWS-ETS fusions are not always sufficient for transformation, and thus differences in cooperating mutations may also contribute to the development of potentially distinct clinical entities [14]. To prove either theory, however, studies are necessary to elicit whether the EWS subtypes differ molecularly through RNA sequencing to assess differences in cell of origin and genetically through DNA or exome sequencing to assess the presence of cooperative mutations. Both analyses could be performed despite limitations in the number of patient samples.

While the underlying pathogenesis of these disease entities likely contribute to their prognoses, it is also important to elicit whether scEWS requires aggressive management given its good prognosis, irrespective of disease pathology. In re-evaluating raw data from a meta-analysis of 61 patients with scEWSs in a study by Delaplace et al. [2], 8 patients had surgical resection alone with negative margins. Of these, only 1/8 (12.5%) developed metastatic disease at a mean follow-up of 39 months (range 11–84 months). Furthermore, of the 10.7% of patients who experienced disease progression in a study by Di Giannatale et al. [3], 10% received intensive chemotherapy and 12% received less intensive chemotherapy. Similarly, Collier et al. [15] found that among patients with adequate local disease control, 90% were alive without relapse among those who received chemotherapy compared to 85.7% without chemotherapy. Among those with inadequate local control, however, the rates of survival without relapse were 66.7 and 0% with and without chemotherapy, respectively [15]. Thus, it is unclear whether chemotherapy is necessary for patients with adequate resection of their scEWS. Furthermore, less intensive regimens may yield similar outcomes to more aggressive chemotherapy regimens in such patients. However, those with inadequate local control are likely to benefit from cytotoxic agents. Prospective clinical trials are necessary to confirm these findings and to identify the appropriate population to treat with surgery alone versus resection with intensive or less intensive chemotherapy.

Conclusions

The prognosis of scEWS is better than that of soft tissue EWS and EWS of the bone. This may be attributed to early detection and/or the presence of distinct biological disease entities. To address this, studies are necessary to elicit whether these EWS subtypes stem from distinct cells of origin and harbor different cooperative mutations. Such studies should also assess how these mutations contribute to differences in disease progression and their metastatic potential. Evaluating the need for cytotoxic agents in completely resected scEWS as well as comparing intensive versus less intensive chemotherapy in such patients could also be accomplished within the context of a larger clinical trial in an attempt to minimize the long-term sequelae of such therapies.

Statement of Ethics

The authors have no ethical conflicts to report.

Disclosure Statement

The authors have no conflicts of interest to report.

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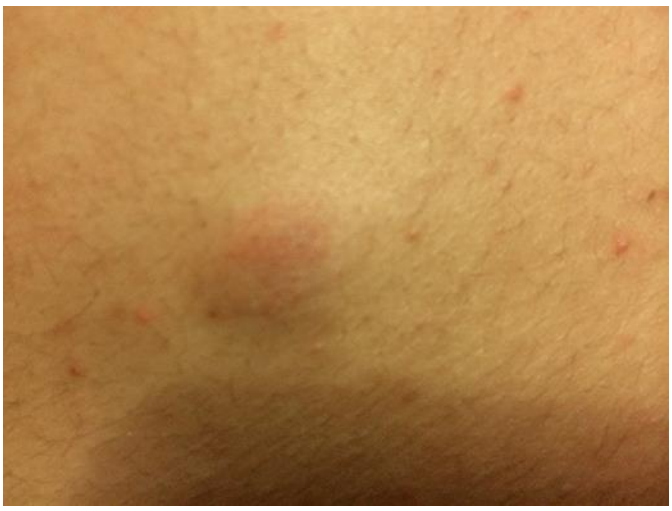

Fig. 1. Primary cutaneous Ewing sarcoma at presentation.