Extraskeletal Ewing's sarcoma in a great toe of a young boy

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Extraskeletal Ewing's sarcoma (EES) is a rare, soft tissue, malignant neoplasm histologically similar to skeletal Ewing's sarcoma. It occurs mainly in adolescents and young adults, and affects extremities in 36% of cases and central locations (commonly paravertebral regions) in the remainder. The differential diagnosis includes other small, blue, round cell tumours. A clinical case of EES involving a great toe in a young boy is reported. EES diagnosis was confirmed by features of histological analysis and immunohistochemistry, and by the presence of the t(11;22) chromosomal translocation.

Key Words: *Ewing's sarcoma; Extraskeletal; Great toe*

Sarcome d'Ewing extrasquelettique au gros orteil chez un garçonnet

Le sarcome d'Ewing extrasquelettique (SEE) est une rare néoplasie des tissus mous semblable au sarcome d'Ewing squelettique sur le plan histologique. Il survient le plus souvent chez les adolescents et les jeunes adultes; il affecte les membres dans 36 % des cas et a une localisation centrale (souvent les régions paravertébrales) dans les autres cas. Le diagnostic différentiel inclut d'autres tumeurs à petites cellules, à cellules rondes et à cellules bleues. On présente ici un cas clinique de SEE affectant le gros orteil d'un garçonnet. Le diagnostic de SEE a été confirmé par la présence d'anomalies caractéristiques aux analyses histologique et immunohistochimique et la présence de la translocation chromosomique t(11;22).

Ewing's sarcoma (ES) is the second most common primary bone malignancy in childhood and adolescence, with an estimated annual incidence of 0.6 per million population (1). It occurs most commonly in the second decade of life. Nearly one-half of all patients are between 10 and 20 years of age, and 70% are younger than 20 years. ES rarely develops in adults older than 30 years or in very young children (2-4). As with many pediatric tumours, ES shows a slight male predominance. Over 95% of cases are characterized by a rearrangement of chromosome 22, generally t(11;22)(q24;q12) translocation, resulting in EWS-FLI1 fusion.

Extraskeletal ES (EES) is a rare soft tissue tumour that is morphologically indistinguishable from the more common skeletal ES. EES commonly affects the extremities, pelvis and soft tissue of the trunk. Often, it is difficult to determine whether a tumour is of bony or soft tissue origin because the bony ES characteristically has extensive soft tissue components, and soft tissue tumours may invade bone secondarily. The time of diagnosis, signs and symptoms are related to the location of the tumour. Pain or swelling (or both) at the site of the primary tumour most often is the presenting symptom (5). The diagnosis of isolated subcutaneous ES in a great toe is extremely rare and, to the authors' knowledge, not reported in the literature at such a young age. Early diagnosis and wide surgical resection combined with current multiagent chemotherapy offer the best disease event-free survival in the absence of distant metastases at diagnosis (6).

CASE PRESENTATION

A four-year-old healthy boy was referred to the plastic surgery clinic. He presented with a solid asymptomatic mass located on the lateral plantar part of his right great toe, that had been growing for three weeks. The presumptive clinical and echographic diagnosis was a lesion of vascular origin.

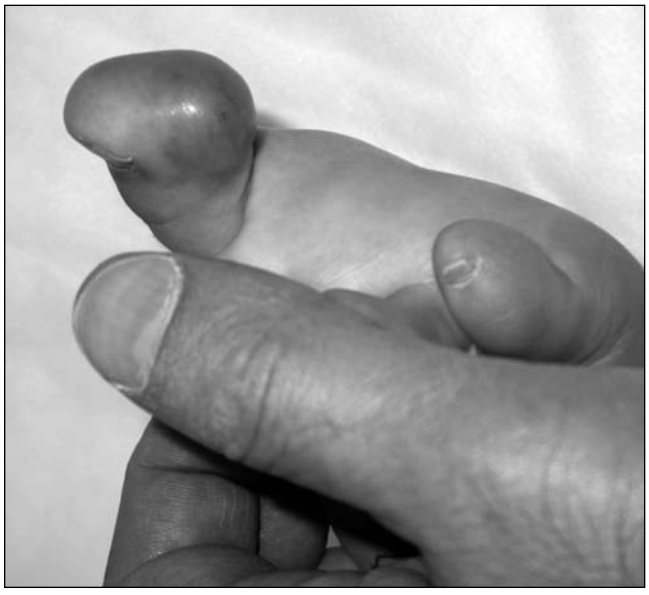

Figure 1) *Extraskeletal Ewing's sarcoma lesion before excisional biopsy*

At this time, the mass was 1.5 cm × 1.25 cm × 0.7 cm, had a slightly compressible pattern and had well-defined edges (Figure 1). After two weeks, the lesion became painful mainly due to rolling between the toes. Because of the increasing size of the lesion and the onset of pain, a surgical biopsy was

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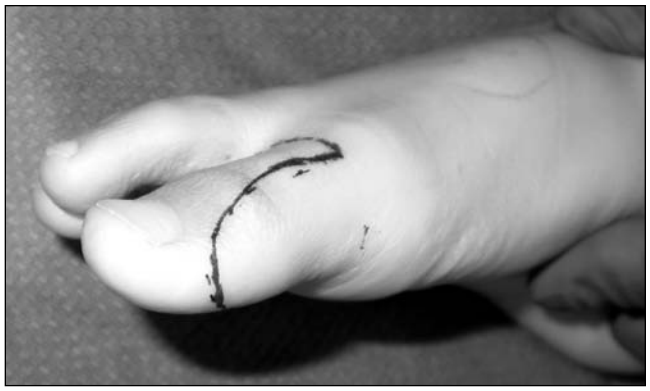

Figure 2) *Surgical plan for definitive amputation*

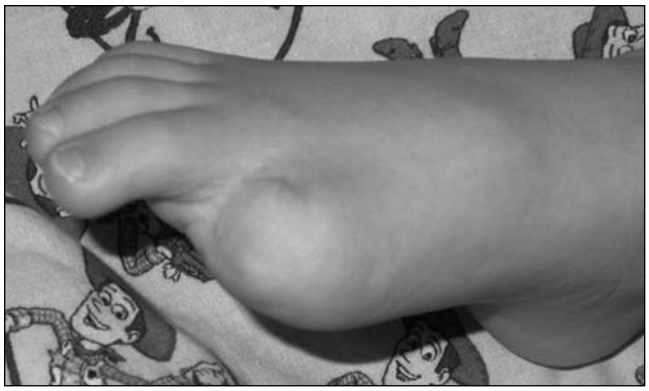

Figure 3) *Final surgical outcome*

planned. The diagnosis of EES/primitive neuroectodermal tumour with EWS-FLI1 translocation was determined by histological and immunohistochemistry examination and reverse transcription-polymerase chain reaction (RT-PCR). The tumour was present at the surgical margins. The patient was referred to pediatric oncology and extended systemic staging was performed. After ruling out disseminated disease, the patient was started on a protocol for localized ES with neoadjuvant chemotherapy consisting of vincristine, doxorubicin, cyclophosphamide, etoposide and ifosfamide (Protocol-POG 9354). Approximately midway through his chemotherapy regimen, further surgery was performed to deal with any residual tumour. After numerous discussions with surgical oncologists and communication with the family, it was elected to carry out an amputation at the metacarpal joint. The lesion was situated such that it approached the periosteum of the proximal phalanx; thus, it was decided that this bone could not be safely left intact. The soft tissue on the medial aspect of the great toe was not involved and could be safely spared and used to cover the amputation stump defect (Figure 2). The first metacarpal was left intact along with its cartilaginous surface. The skin flap was based proximally on the medial aspect of the great toe, and measured 2 cm in length. A tension-free stump closure was achieved. Wound healing was uneventful (Figure 3) and his course of chemotherapy was resumed as per protocol. The surgical specimen demonstrated no residual tumour.

DISCUSSION

ES is a malignant, small, round cell tumour of the bone, and was first described by James Ewing in 1921 (7) as an osteolytic lesion of the radius in a 14-year-old girl. EES was first described by Tefft et al in 1969 (8). EES is a rare but highly malignant tumour, and accounts for approximately 5% of all soft tissue sarcomas in childhood (9). Although the histogenetic origin of ES has been ascribed over the decades to endothelial, mesenchymal and hematopoietic stem cells, recent evidence from immunocytochemical, cytogenetic and molecular genetic investigations indicates a neural crest origin for ES (10-19). Derivation from a primitive, pluripotent, neural crest cell line is supported by the fact that these tumours synthesize acetylcholine transferase, which is essential to acetylcholine synthesis (12,13,18). Because of their ability to synthesize acetylcholine transferase and the lack of appreciable synthesis of adrenergic pathway precursors, ES is believed to be derived from postganglionic parasympathetic primordial cells located throughout the parasympathetic autonomic nervous system. The variety of soft tissue and bony locations may be explained in part by the wide distribution of these pluripotent stem cells throughout the parasympathetic autonomic nervous system.

The differential diagnosis of small, round cell tumours is difficult, and many techniques, such as histochemical stains, immunohistochemistry, electron microscopy and molecular analysis, must be used to arrive at an accurate diagnosis (20). In the present case, we used RT-PCR to detect the translocation that involves the ES gene (EWS) on chromosome 22 and a member of the ETS family of genes (FLI1 on chromosome 11), confirming the diagnosis of EES and primitive neuroectodermal tumour. This chromosomal translocation (EWS-FLI1) is present in 90% to 95% of the tumours in the ES family. The second most common translocation is EWS-RGE [t(21;22)(q22;q12)], which occurs in 5% to 10% of tumours. The t(11;22)(q24;q12) chromosomal translocation present in the majority of the ES results in rearrangement of the FLI1 gene with fusion of the carboxy-terminal region of FLI1 with the amino-terminal region of EWS. Because the EWS domain is substituted for a portion of the FLI1 transcriptional domain, the EWS-FLI1 fusion alters the transcriptional activation property usually associated with FLI1.

RT-PCR for EWS-FLI1 and EWS-ERG fusion transcripts may provide the diagnostic information necessary to confirm the histopathological suspicion of ES in certain cases (21-27). The benefit of RT-PCR is that detection of a t(11;22) or t(21;22) translocation may be performed in a considerably shortened period when compared with cytogenetic culture means. In addition, certain tumours without chromosome 11;21 or 11;22 abnormalities may express hybrid transcripts that are detected only by RT-PCR or other molecular techniques. Aspiration or fine-needle biopsies of tumours may be evaluated readily by RT-PCR to confirm the diagnosis of ES (26,28-30). Furthermore, the histochemical and immunohistochemical stains support the diagnosis of EES based on nonimmunoreactivity of the tumour cells for epithelial, lymphoid, vascular, neural and neuroendocrine markers.

The data compiled from patients with ES revealed that the primary sites were divided almost evenly between the extremities (50%), and the central axis (48%) and skull (2%) (5). The extremity tumours were distal in 52% and proximal in 48%. The central axis tumours were of the pelvis (45%), chest wall (34%), spine and paravertebral region (12%), and head or neck (9%) (4,5). EES occurred in the extremities in 36% of cases and in central locations in the remainder. Often, determining whether a tumour is of bony or soft tissue origin is

difficult, because the bony ES characteristically has an extensive soft tissue component, and a soft tissue tumour may invade bone secondarily.

The diagnostic imaging evaluation should consist of a thorough examination of the primary site and a search for metastatic disease. The importance of fully defining the extent of disease at the primary site before therapy cannot be overemphasized. The planning and delivery of optimal local therapy require documentation of the initial extent of the tumour, which can be expected to decrease after chemotherapy. Plain films, magnetic resonance imaging of the primary site, computed tomography of the chest and bone scans are necessary for the staging workup for the ES. In the past, treatment modalities used for ES in children were radiotherapy, surgery or a combination of both. With local treatment alone and radiation, the tumour control rates vary from 44% to 80%. However, the metastatic rate observed in the first two years was 75% to 85% and, therefore, long-term survivors were only exceptional (31). With the advent of multidrug chemotherapy in combination with radiotherapy, the five-year survival rate increased to 55% to 70% in patients with localized tumours (32-35) and the local control rate was above 90% (32-34,36). However, high doses of radiotherapy have induced long-term side effects. Although the results in terms of survival have not improved after the introduction of neoadjuvant chemotherapy, lower doses of radiotherapy led to diminished late side effects of this treatment (37).

The typical management of ES begins with neoadjuvant chemotherapy followed by local control and then additional systemic chemotherapy (38). Combination chemotherapy with vincristine, doxorubicin, cyclophosphamide and actinomycin D has been standard for several years. Clinical trials in the 1980s focused on the addition of ifosfamide, with or without etoposide. Results from single-arm studies comparing outcome with historical controls are conflicting, but the only randomized trial demonstrated that the addition of ifosfamide and etoposide to vincristine, doxorubicin, cyclophosphamide and actinomycin D resulted in a significant improvement in event-free survival (39).

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