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Navigating the Diagnostic Maze: A Case Report of Uncommon Cardiac Metastasis in Childhood Ewing Sarcoma

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Abstract

Ewing sarcoma is a bone cancer affecting children and young adult males. It usually presents as a single bone tumor, but it can also occur in multiple locations. Nevertheless, Ewing sarcoma is an extremely aggressive tumor capable of metastasizing to other parts of the body, such as the lungs, bones, liver, and lymph nodes. Cardiac metastases are rare, indicating a poor prognosis, as they suggest that the cancer has become more advanced and challenging to treat.

This case report describes a 9-year-old boy who presented with complaints of fever and multiple swellings in the calvaria, periorbital region, clavicle, and left thigh. Laboratory investigations revealed a high erythrocyte sedimentation rate, elevated absolute neutrophil count, high phosphate and calcium levels, and low magnesium levels. Computed tomography imaging revealed the presence of multifocal osseous expansile lytic lesions, multiple pulmonary metastases, and extensive soft tissue involvement of the heart. Based on these findings, possible differential diagnoses of Langerhans cell histiocytosis, lymphoma, and Ewing sarcoma were considered. Further histopathological examination and immunohistochemistry confirmed a final diagnosis of metastatic Ewing sarcoma.

The most common metastasis sites for Ewing sarcoma are the lungs, with rare occurrences in the central nervous system, and metastasis to the heart is uncommon. We present here a rare undiagnosed Ewing sarcoma with cardiac metastasis, in addition to pulmonary and multifocal osseous metastasis. This case is unique because multifocal osseous involvement is rare and further lung and heart involvement is even rarer in Ewing sarcoma.

Keywords

- Ewing sarcoma
- multifocal osseous metastasis
- lung metastasis
- cardiac metastasis
- case report

Introduction

Ewing sarcoma or primitive neuroectodermal tumor (ES/PNET) is a rare and aggressive sarcoma involving the soft tissues or bones in children and young adults that can metastasize quickly.[1–5] James R. Ewing, an American pathologist, first described this condition in 1921.[6] The incidence of the tumor is only 1 to 3 cases per million per year.[7] It is more

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common in Caucasians than in Asians or Africans. ES/PNET usually occurs in the diaphysis or metaphyseal-diaphyseal portion of the pelvis, ribs, and long bones and radiologically appears as an ill-defined osteolytic lesion with permeative or moth-eaten bony destruction and periosteal reaction. In the axial skeleton, the sacrum and lumbar spine are the most commonly affected sites.[8] The most prevalent symptoms are pain and fever, with frequently observed laboratory results comprising leukocytosis, anemia, and an elevated erythrocyte sedimentation rate.[9–11] Around 85% of cases show fusion between the EWSR1 and FLI1 gene, forming chimeric genes that promote tumorigenesis.[12] In a study conducted by Khanna et al, around 20 to 25% of patients have already developed metastasis at the time of diagnosis.[13] ES usually metastasizes to the lungs and rarely to the nervous system. Although few reported cases of ES metastasizing to the heart have been described in the literature,[14,15] this case report discusses one such case where the patient had an undiagnosed ES and presented with multifocal cardiac, pulmonary, and bony metastases.

Case Report

A 9-year-old boy presented to pediatric medicine with a history of prolonged episodes of moderate to high-grade fever lasting for about 6 months, accompanied by chills and rigors. The fever episodes were intermittent and relieved by medication, although not well documented. The child's mother also observed the later development of multiple swellings in different body parts, starting with the left thigh and progressing to the scalp, orbit, and calvarium over 2 months. These swellings increased in size and number and were associated with persistent pain and overall weight loss. The patient had a pathological left femur bone fracture, for which a Plaster of Paris cast was applied. He also had a history of nonproductive cough but reported no breathlessness or hemoptysis. The patient had no cardiac-related complaints.

Upon examination, the child displayed poor general condition with pallor. Local examination revealed multiple scalp swellings in the calvaria, swelling involving the right periorbital region, leading to proptosis. Blood investigations indicated anemia, leukocytosis, elevated absolute neutrophil count, a high erythrocyte sedimentation rate, and electrolyte imbalances, including elevated phosphate and calcium levels and low magnesium. Additionally, lactate dehydrogenase and uric acid levels were elevated. An orthopaedic opinion was sought for the left femur fracture, and a high groin slab was applied. Ophthalmic examination revealed proptosis of the right eyeball with lagophthalmos. X-rays revealed ill-defined lytic lesions in both the femur and skull. Based on the clinical findings, provisional diagnoses of metastatic neuroblastoma, rhabdomyosarcoma, lymphoma, and metastatic ES were made. A computed tomography (CT) scan (►**Fig. 1A**) showed multiple lytic destructive bony lesions with exuberant enhancing necrotic soft tissue components at multiple bony sites, including cranial bones, the periorbital region, the neck and proximal shaft of the left femur, and the right superior pubic bone. Similar lesions were also noted in numerous ribs, the clavicle, and the left humerus (not shown in the figures). Additionally, multiple variable-sized enhancing nodules were noted in both lungs. Soft tissue involvement was observed in the form of nodular enhancing lesions in the left arm, the lateral chest wall, and the subcutaneous plane of the left arm (images not included). CT images of the thorax also showed diffuse irregular enhancing soft tissue involving the endo-myocardium, projecting into the cardiac lumen, predominantly in the bilateral ventricles, and infiltrating into the adjacent pericardial lining (►**Fig. 1C**). Similar enhancing soft tissue was also observed along the pericardial tissue around the ascending aorta and pulmonary trunk (►**Fig. 1B**).

Based on the clinical and radiological observations, extensive cardiac involvement, and multiple bony lesions, the differential diagnoses of Langerhans cell histiocytosis and metastatic ES were considered.

An ultrasound-guided core needle biopsy of the left clavicular swelling was performed, revealing linear cores of fibrocollagenous tissue and fibromuscular tissue infiltrated with tumor arranged in diffuse sheets and focal rosette patterns (►**Fig. 2A** and **B**, asterisk). Adjacent skeletal muscle was also infiltrated by tumor cells of similar morphology (►**Fig. 2A**, black arrow). These tumor cells were round to oval with minimal pleomorphism, a high nucleus-to-cytoplasm (N:C) ratio, coarse chromatin, inconspicuous nucleoli, and a scant amount of cytoplasm. Apoptotic bodies were present, and conspicuous mitotic activity was noted. Following the hematoxylin and eosin staining, an immunohistochemical study was performed. Immunohistochemical staining for CD99, neuron-specific enolase, and FLI-1 were positive, while leukocyte common antigen, synaptophysin, CD-56, and desmin were negative—suggestive of ES. Unfortunately, whole-body magnetic resonance imaging, 18 fluorodeoxyglucose positron emission tomography-CT, and technetium-99m methylene diphosphonate skeletal scintigraphy could not be performed due to the patient's precarious condition and poor Glasgow Coma Scale. Later, the child developed acute respiratory distress and eventually passed away due to cardiorespiratory arrest.

Discussion

ES is a primary malignant bone tumor originating from cells in the bone marrow's connective tissue. It is classified as diffuse endothelioma of bone or endothelial myeloma and is characterized by a distinctive radiographic appearance, as described by James Ewing.[6] As per Oberling,[16] ES originated from the marrow stem cell and is grouped with myeloma and non-Hodgkin's lymphoma as a round cell tumor with a predilection for the marrow-rich diaphysis. Pathological and molecular similarities among several related tumors have been observed, including primary ES, extraosseous ES, Askin, and peripheral PNET. Collectively, these tumors are referred to as the ES family of tumors. ES is the second most common primary malignant bone tumor in childhood and adolescence, following osteosarcoma. It is the fourth

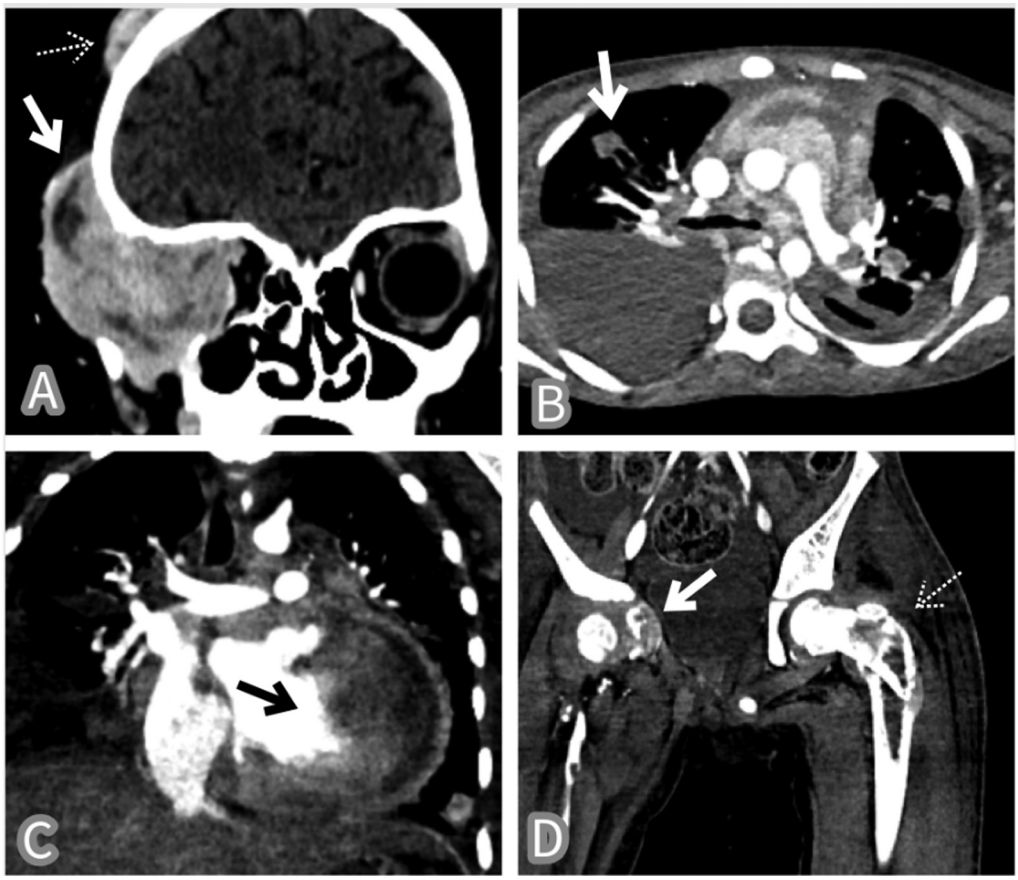

Fig. 1 Contrast-enhanced computed tomography (CECT) images showing lesions involving orbit (**A**, solid arrow), calvaria (**A**, dotted arrow), bilateral lungs (**B**, white arrow), endo-myocardium (**C**, black arrow), pubic ramus (**D**, solid arrow), and femur (**D**, dotted arrow). Images (**B**) and (**C**) show extensive endomyocardial involvement.

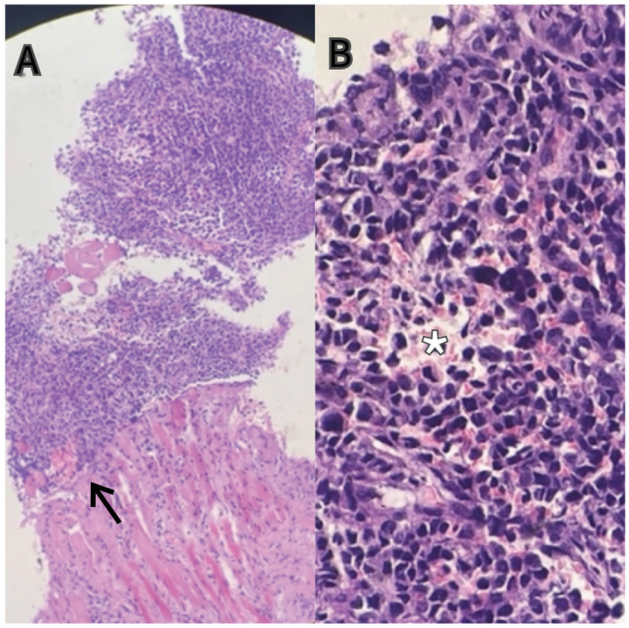

Fig. 2 Photomicrograph (hematoxylin and eosin [H and E] stain). (**A**) Low-power image showing linear cores of fibrocollagenous tissue, with adjacent skeletal muscles (**A**, black arrow) infiltrated by tumor cells arranged in diffuse sheets and focal rosette patterns (**B**, high power image–asterisks).

most common primary malignant bone tumor overall, after myeloma, osteosarcoma, and chondrosarcoma (in descending order of incidence). The average age of diagnosis for ES is in the second decade of life, with the youngest reported patient being 5 months old[17] and the oldest around 83 years.[18] Peak prevalence occurs between 10 and 15 years, with a slight male predilection (male-to-female ratio of 1.5:1).[11] The metastatic form of the tumor has a poor prognosis; however, patients with only pulmonary metastasis have a better prognosis than those with bone, bone marrow, or cardiac metastasis. In most studies, the 5-year survival rate for patients with only pulmonary metastasis ranges from 30 to 40%.[7] For patients with bone or marrow metastasis, the 5-year survival rate is less than 20%.[7] The molecular trigger for ES is a chromosomal translocation that fuses the EWSR1 (Ewing sarcoma RNA binding protein 1) gene with one of the five genes from ETS (E-twenty-six) family: FLI1 (Friend leukemia integration-1 transcription factor), ERG (erythroblast transformation-specific related gene), ETV1 (erythroblast transformation-specific variant transcription factor 1), ETV4, and FEV.[13,18] The specific translocations responsible for these fusions are as follows: (1) t(11;22)(q24;q12), resulting in the fusion gene EWSR1-FLI1 (85%); (2) t(21;22)(q22;q12), leading to the fusion gene EWSR1-ERG (10%); (3) t(7;22)(q22;q12), yielding the fusion gene EWSR1-ETV1 (< 1%); (4) t(17;22)(q21;q12), giving rise

to the fusion gene EWSR1-ETV4 (< 1%); and (5) t(2,22)(q35; q12), generating the fusion gene EWS1-FEV (again, < 1%).[9] The resulting fusion gene is responsible for tumorigenesis. Patients typically present with a mass or pain with swelling being the most consistent presenting complaint.[19] The pain is initially dull but becomes severe and persistent. Other symptoms may include fever, malaise, and weight loss,[20] as observed in our case. Blood tests may reveal anemia, leukocytosis, and elevated lactate dehydrogenase levels.[9,10] ES is one of the malignant tumors that presents with symptoms mimicking infection.[20] Local elevated temperature, dilated veins, and tenderness suggest an inflammatory condition, which can be due to increased tumor growth leading to outgrowth of its blood supply, resulting in extensive necrosis.[21]

X-rays of the tumor site usually show destructive changes to the affected bone along with "onionskin" periostitis. ES has a wide range of skeletal manifestations. The femur and ilium are the commonly affected bones, which are also seen in our case; the tibia, humerus, fibula, ribs, and sacrum are involved in varying percentages.[11] The clavicle and facial bones are affected in less than 1% of cases,[11] and these areas are involved in our case as well. Proximal long tubular bones are more commonly involved than distal long tubular bone, with most long bone lesions being meta-diaphyseal rather than pure diaphyseal.[11] Pathologic fractures as an initial clinical presentation are uncommon[11]; however, our case presented with a pathological fracture of the femur. CT scans of the lungs and whole body aid in detecting lung, heart, and bone metastasis.[11] Common sites for metastasis include the lungs, bones, and bone marrow.[9,11] Skeletal metastases can occur early, resulting in extensive lytic bony destruction. ES is the most common primary malignant bone tumor to metastasize to bone,[22] with the spine being a common site.[23] As in osteosarcoma, ES can also cause multiple skip lesions within the same bone.[24] Lung metastasis is also common.[22] This case report discusses an uncommon case of ES metastasizing to the heart. Such occurrences are rare, with only a few documented cases.[14,15] The primary concerns with cardiac metastasis include the potential for embolization, sudden cardiac death, and hemodynamic instability. In children, secondary cardiac tumors are infrequent compared with adults, with sarcomas and lymphomas being the most common primary neoplasms that metastasize to the heart.[25] Symptoms of cardiac tumors can include dyspnea, arrhythmias, syncope, or signs of heart failure due to obstruction of right ventricular blood inflow.[25,26] Left-sided tumors may also lead to stroke if emboli travel to the brain.[25]

The gold standard for diagnosing ES involves identifying chromosomal translocations using fluorescence in situ hybridization and polymerase chain reaction. Unfortunately, these molecular diagnostics are rarely used in resource-constrained settings.[9,27]

Prognostic factors that worsen the outlook for ES include the presence of multiple metastases, systemic symptoms, leukocytosis, elevated lactate dehydrogenase levels, tumor size greater than 8 cm, tumor volume exceeding 200 mL, and tumor site (pelvis).[28]

The ES family of tumors share common chromosomal translocations.[29]

The treatment for ES involves a multimodal approach, including surgery, systemic chemotherapy, and radiotherapy. Improvements in treatment techniques have resulted in enhanced outcomes, with a 5-year event-free survival rate of 60 to 70%.[9,30] However, late recurrences, occurring more than a decade after initial treatment, remain a challenge. Unfortunately, there is no established standard treatment strategy for recurrent ES, and the 5-year survival rate remains below 20% for patients with recurrent or metastatic tumors.[9,30]

ES frequently metastasizes to the lung, while cranial metastasis remains rare, occurring in only 1% of cases. Cardiac metastasis is even more exceptional and has been reported in only a few cases.[15] Remember that ES is a complex disease, and understanding its molecular pathways and metastatic patterns is crucial for developing effective treatment strategies.

ES is a highly malignant bone tumor with a poor prognosis. The prognosis has improved over the years for localized tumors but remains poor for patients with metastatic disease. It is uncommon to have multiple calvarial lesions from ES. Although it is known that ES commonly metastasizes to the lungs and rarely to the central nervous system and skull, we should be aware that ES can also infrequently metastasize to the heart. ES most commonly presents with complaints of fever, bone pain, and rarely with pathological fractures, thus posing the diagnostic dilemma with osteomyelitis infection. We report a rare case of undiagnosed ES with multiple bone, lung, cardiac, and subcutaneous metastasis.

Declaration of Patient Consent Form

Written informed consent was obtained from the patient's parents for the publication of this case report and any accompanying images.

Conflict of Interest

None declared.

Acknowledgment

None.

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