A 13-year-old boy presented to an outside hospital with complaints of intermittent left hip pain after playing football. The patient was thought to have a muscle strain. He was prescribed non-steroidal anti-inflammatory drugs for symptomatic relief, with instructions to temporarily abstain from vigorous sports activities.

However, the hip pain persisted. He presented 3 months later to the current authors’ institution with the same complaints. He denied any history of trauma, fever or chills, weight loss, or other symptoms. His medical history was unremarkable. He was not taking any medications at that time.
The patient was afebrile and in no apparent distress. There was some tenderness with active motion of the left hip and some fullness of the left ilium. A mass was appreciable on palpation in the left lower quadrant of the abdomen. His neurologic status was intact. Strength and range of motion (ROM) in all lower extremity joints were within normal limits. The rest of his physical examination was unremarkable.

An anteroposterior (AP) radiograph of the pelvis was obtained. Subsequently, additional radiographic studies including magnetic resonance imaging (MRI) were done (Figs 1–5).

Based on the history, physical examination and imaging studies, what is the differential diagnosis?
RADIOGRAPHIC INTERPRETATION

The AP radiograph (Fig 1) shows a large, predominantly lytic lesion with a well-demarcated margin involving the superior half of the left iliac bone. Coronal (Fig 2) and axial (Fig 3) T2-weighted MRI scans show tumor of mixed intermediate and high signal intensity and a soft tissue mass. The focal high signal in these images indicates liquefaction necrosis or hemorrhage. The linear dark signal along the anterior border of this area could represent a thin calcific shell. Axial T1-weighted sequences with fat saturation before (Fig 4) and after (Fig 5) intravenous administration of gadolinium-diethylenetriaminepentaacetic acid show enhancement of the tumor in the bone. Axial images also show extension of tumor to the iliac side of the sacroiliac joint. The cortical irregularity and vague periosteal enhancement along the posterior margin of the ilium also are clearly visible.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis based on the radiograph:
- Ewing’s sarcoma
- Aneurysmal bone cyst
- Langerhans cell histiocytosis
- Fibrous dysplasia
- Infection
- Osteosarcoma
- Telangiectatic osteosarcoma
- Lymphoma

An open incisional biopsy with intraoperative frozen section was done (Figs 6–8).

Based on the history, physical findings, radiographic studies, and histologic pictures, what is the diagnosis and how should this lesion be treated?
**Fig 6.** Low power photomicrograph (Stain, hematoxylin and eosin; original magnification, ×200).

**Fig 7.** High power photomicrograph (Stain, hematoxylin and eosin; original magnification, ×400).
**Fig 8.** MIC-2 immunohistochemical stain, high power photomicrograph (Original magnification, ×400).

*See page 337 for diagnosis and treatment for the lesion.*
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HISTOLOGY
Grossly, the soft tissue component of the specimen was hemorrhagic and gray. Histologic examination revealed monotonous sheets of cells admixed with much larger zones of coagulative necrosis (Fig 6, low power). Higher power magnification showed malignant small cells of uniform size, characterized by round to oval nuclei, a high nuclear to cytoplasmic ratio, and finely stippled chromatin with small to moderate-sized nucleoli (Fig 7, high power). Some mitotic figures were present. Periodic acid Schiff stains with and without diastase revealed abundant cytoplasmic glycogen. Immunohistochemical stains were positive for vimentin and CD99 (Fig 8). Staining for leukocyte common antigen, cytokeratin AE1, S-100, and T and B cell markers were negative.

DIAGNOSIS
Ewing’s sarcoma of the pelvis

DISCUSSION
Ewing’s sarcoma is the second most common primary malignant bone tumor in childhood and adolescence after osteosarcoma, with a reported incidence of 2.1 per one million children and a slight male preponderance.29,31 It occurs most commonly in the second decade of life. No causative or etiologic factors for Ewing’s sarcoma have been identified. Rarely, it has been reported to develop after chemotherapy.26 Ewing originally described this tumor in 1921 and differentiated it from lymphoma.11 It now is known that Ewing’s sarcoma belongs to the primitive neuroectodermal tumor family. Various chromosomal abnormalities have been described for Ewing’s sarcoma, but the most common (in > 90% of the cases) is a translocation between chromosomes 11 and 22 known as t(11;22).27 The fusion protein, designated as EWS-FL1 has DNA-binding activity of FL1, but is under the regulation of EWS gene promoters. The EWS-FL1 protein is capable of malignant transformation in murine fibroblast cell lines.8

The most common presenting complaints are pain and swelling of the affected region.30 Systemic signs and symptoms such as fever and weight loss also can occur, especially in patients with metastatic disease. Because of the nonspecific nature of complaints, there usually is a delay of diagnosis for many weeks to months in a large proportion of the patients.12 The tumor can present almost anywhere in the body. Unlike osteosarcoma, Ewing’s sarcoma often begins in the diaphysis of long bones. In a series of 303 patients, the most common sites of occurrence were the pelvis (21%), femur (20%), tibia (10%), and humerus (10%).15 Approximately ¼ of the patients present with metastases, and the most common sites of metastases are lung (50%), bone (25%), and bone marrow (20%).20

Initially, the current patient had induction chemotherapy with vincristine, doxorubicin, and cyclophosphamide. Reconstruction of the pelvis then was done after resection of the tumor with wide margins. Histologic examination revealed extensive and near-complete coagulative tumor necrosis (> 99% necrosis). Radiographs of the specimen taken after chemotherapy and wide resection showed the tumor margin, which was geographic in some areas and poorly defined in others (Fig 9). An AP radiograph (Fig 10) taken after limb salvage surgery showed screws and fibular bone graft extending from the sacrum and buttressing the left acetabulum. At last followup 76 months after surgery, the patient was disease-free and able to walk without crutches. He had full range of hip motion and no pain.

The histologic features of Ewing’s sarcoma are characterized by sheets of primitive monomorphic cells with a high nuclear to cytoplasmic ratio.9 As a prototype of the pediatric undifferentiated small blue cell tumor, Ewing’s sarcoma classically is arrayed in featureless sheets of cells usually associated with areas of necrosis. The nuclei are primitive, with finely distributed chromatin and inconspicuous nu-
cleoli. There usually is little to moderate cytoplasm, and mitotic activity often is moderate or low. Most of these tumors are rich in cytoplasmic glycogen, which can be shown with periodic acid Schiff stains. However, this feature is of little diagnostic help, because a small number of Ewing's sarcomas may have little or no stainable glycogen, and other sarcomas in pediatric patients also can have stainable glycogen. Electron microscopic examination typically reveals a paucity of organelles, and the presence of glycogen (although akin to periodic acid Schiff stains, a small percentage is negative).

Immunohistochemical demonstration of perimembranous staining for CD99 (MIC-2) is highly sensitive for Ewing's sarcoma/primitive neuroectodermal tumor, but occasionally may be seen in nonHodgkin's lymphomas, which can closely mimic the histologic appearance of Ewing's sarcoma. Showing the EWS-FL1 gene fusion by molecular methods, typically done on fresh or frozen tissue by RT-PCR, now is proving to be a sensitive and specific method of establishing the correct diagnosis.

There is no universally accepted staging system for Ewing's sarcoma. However, staging is based on imaging modalities used to evaluate the primary tumor and its likely site of metastasis. Plain radiographs, MRI scans, computed tomography (CT) scans of the lungs, and bone scans can be used to determine the extent of the disease. Bone marrow biopsy may be used to rule out tumor infiltration. Laboratory workup should include complete blood count and erythrocyte sedimentation rate (abnormal in approximately 50% of the patients).

The classic appearance of Ewing's sarcoma on conventional radiographs is a permeative, destructive lesion with lamellated periosteal reaction (onion skinning) and a soft tissue mass. The radiographic appearance of Ewing's sarcoma, however, often varies from this classic appearance and the tumor may be lytic, mixed lytic and blastic, or predominantly sclerotic. The tumor margin may be somewhat geographic, as in the current patient, but is more likely ill-defined, indicating the aggressive nature of the tumor. Similarly, the associated periosteal reaction, which also reflects the aggressiveness of the tumor, may be lamellated, spiculated with a "hair on end" appearance, or continuous. Magnetic resonance imaging is the most sensitive imaging modality to show the
extent of the tumor\textsuperscript{3,14,28} and is helpful in determining the differential diagnosis, treatment, and resectability of the tumor. On MRI scans, Ewing’s sarcoma usually has a low signal on T1-weighted sequences and a high signal on T2-weighted sequences, and it enhances with gadolinium. It is not uncommon for an associated soft tissue mass to be present with bone involvement. In the current patient, the plain radiographic appearance was nonspecific, but suggested an aggressive process. The MRI scan showed the presence of a soft tissue mass, which greatly narrowed the differential diagnosis. The MRI scan also clearly showed the tumor extending to the iliac side of the sacroiliac joint and the absence of involvement of the neurovascular bundle.

A large study of 975 patients with Ewing’s sarcoma showed that the biggest prognostic factor is the presence of metastases at the time of diagnosis.\textsuperscript{7} The study showed that for patients with metastases, lung involvement was associated with a better prognosis than bone metastases. Other poor prognostic factors include tumor size greater than 8 cm, pelvic location, age older than 17 years, and high levels of lactate dehydrogenase.\textsuperscript{1} Good radiologic and pathologic response to induction chemotherapy is a favorable prognostic factor.

The goal of therapy in Ewing’s sarcoma is aimed at local control and treatment of metastatic disease. Local control can be attempted through surgery with or without radiation. Generally, presurgical chemotherapy is administered to reduce tumor volume. It also allows the oncologist to observe the response to chemotherapy and begin a systemic therapy immediately to treat micrometastatic disease. This approach has been shown to improve local control and survival.\textsuperscript{24}

In the past, there was controversy whether surgery actually improved overall survival in patients with Ewing’s sarcoma.\textsuperscript{18} However, it was suggested that if resection of the tumor with wide margins can be achieved, then surgery can play an important role in control of the disease.\textsuperscript{22,23} In many centers, surgery and chemotherapy are combined. However, in patients in whom these tumors are large, such surgical procedures can result in significant morbidity because they are present in functionally important areas.

Radiation therapy has been associated with a 10% to 30% incidence of second primary bone tumors, especially sarcomas, at 20 years followup.\textsuperscript{16,25} Therefore, some institutions use radiation much less often to obtain local control, especially in children.

Chemotherapy for patients with Ewing’s sarcoma continues to evolve. The First Intergroup Study of Ewing’s Sarcoma (1973–1978) showed the addition of doxorubicin to triple therapy (vincristine, dactinomycin, cyclophosphamide) in patients with nonmetastatic disease resulted in a 60% survival at 5 years, compared with 44% in patients treated with pulmonary radiation and triple therapy.\textsuperscript{19} Interestingly, patients with pelvic tumors did not benefit from the regimen. The Second Intergroup Study of Ewing’s Sarcoma (1978–1982) showed that intermittent high-dose therapy with vincristine, doxorubicin, cyclophosphamide and dactinomycin was superior to continuous moderate dose therapy with these agents.\textsuperscript{10} Together, the results of these studies indicate that patients with metastatic disease have a poorer prognosis when compared with patients with nonmetastatic disease.\textsuperscript{5} A Third Intergroup Study of Ewing’s Sarcoma compared the vincristine, doxorubicin, cyclophosphamide, dactinomycin regimen with and without addition of ifosfamide-etoposide. The combination therapy seems to be superior to the vincristine, doxorubicin, cyclophosphamide, dactinomycin regimen alone.\textsuperscript{13,21} Currently, a Fourth Intergroup Study of Ewing’s Sarcoma is underway, comparing the efficacy of a dose-intensified 30-week versus a regular 48-week course of vincristine, doxorubicin, cyclophosphamide, dactinomycin, and ifosfamide-etoposide in patients with localized disease. Although the aforementioned developments are encouraging, it seems that despite intensive chemotherapy, the prognosis of patients with nonmetastatic pelvic Ewing’s sarcoma has not improved dramatically within the past...
decade. Patients with metastatic disease have an even worse prognosis.

To date, the data suggest that there is no good therapy for patients who have a relapse while receiving chemotherapy. High-dose chemotherapy with hematopoietic stem-cell transplantation has provided mixed results.4,17

Given the young age of the current patient and the large size of the tumor, the tumor first was shrunk with five rounds of chemotherapy. Next, a wide resection of the tumor with an extraarticular resection through the ala of the acetabulum was done. Microscopic examination of the resected specimen revealed extensive, near complete (> 99%) necrosis, consistent with an effective chemotherapeutic effect, and no evidence of tumor at the operative margins. A left free fibular microvascular bone graft was done to reconstruct the pelvis.

In followup, the patient recovered from surgery and finished chemotherapy without complications. The patient remains disease-free at 76 months after surgery.

From a diagnostic and treatment point of view, Ewing’s sarcoma presents a challenge to the physician and surgeon. Today, therapy is multimodal and empirically derived. Patients with Ewing’s sarcoma should be referred to major cancer centers. New advances in molecular biology will be important in directing therapies in the future.

References