Chronic Bilateral Thigh and Knee Discomfort in an 18-year-old Man

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History and Physical Examination

An 18-year-old man presented with severe, intermittent bilateral thigh and knee pain of approximately 6 months' duration. His symptoms had initially manifested as localized anterior left knee pain 2 years earlier, and he had been treated with high-dose ibuprofen and physical therapy for the presumptive diagnosis of patellofemoral syndrome. Despite attempts at nonoperative management, he had experienced progressive discomfort involving the left thigh, right knee, and right thigh. At the time of presentation, he described pain principally in the left thigh, characterized as self-remitting and without clear antecedent. He also noted long-standing night pain interfering with sleep but denied any fevers, chills, rigors, weight loss, or other constitutional symptoms. A review of systems was otherwise negative, and medical history was unremarkable.

Physical examination revealed mildly shortened stance phase with respect to the left lower extremity; the patient noted his limp had been more pronounced during the preceding month. Pelvic compression and palpation along the

spinal column and long bones of the lower extremities elicited no focal tenderness. No visible lesions or palpable masses were observed in the trunk or upper or lower extremities. Active and passive range of motion of the hips and knees were full and well tolerated. The patient was neurologically intact with normal sensation to light touch and full motor strength in all muscle groups.

Laboratory studies revealed normal white blood cell count (6.08 K/ μ L [normal 4.0–11.0]), platelet count (315 K/ μ L [normal 150–400]), hemoglobin (15.6 g/dL [normal 13.5–17.5]), lactate dehydrogenase (156 U/L [normal 100–220]), alkaline phosphatase (118 U/L [normal 50–350]), and calcium level (10.3 mg/dL [normal 8.5–10.5]). Blood urea nitrogen was elevated minimally (21 mg/dL [normal 5–20]).

Plain radiographs of the left femur (Fig. 1), computerized tomography (CT) scan of the pelvis and bilateral femora, radionuclide scan (Fig. 2), and magnetic resonance imaging (MRI) of the right acetabulum and bilateral femora (Fig. 3) were obtained.

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

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Imaging Interpretation

Radiographs of the left femur (Fig. 1) revealed an osteolytic lesion extending from the intertrochanteric region to the middiaphysis. The lesion demonstrated mild bony remodeling and cortical thickening most evident in the diaphysis with a well-defined proximal margin.

A noncontrast CT scan performed through the pelvis and bilateral femora demonstrated multifocal osteolytic lesions in the left femur, right femur, and superior right

Fig. 1A–B Anteroposterior radiographs of the (A) proximal and (B) distal left femur demonstrate an extensive, well-margined osteolytic lesion with involvement from the intertrochanteric region to the middiaphysis. Cortical thickening and remodeling are evident along the diaphysis.

acetabulum. The left femoral lesion (34 cm in length, from the basicervical region to distal diaphysis) was associated with a thin, circumferential mantle of periosteal reaction. Within the intertrochanteric region, the left femoral lesion occupied the entire intramedullary cavity; there was no evidence of extension into trochanteric subchondral bone, and no definite matrix calcifications could be seen. Osteolytic foci with similar attenuation and well-defined margins were observed in the right femur (7 cm in length, from the femoral neck to proximal diaphysis) and superior right acetabulum (2.6 cm × 2.8 cm × 2.8 cm).

Whole-body radionuclide scintigraphy (Fig. 2) indicated multifocal increased tracer uptake involving the left femur (proximal femur through distal diaphysis), the right proximal femur, and the anterior aspect of the left eighth rib.

MRI scan of the pelvis and bilateral femora (Fig. 3) demonstrated low T1 signal intensity, high T2 signal intensity, and postgadolinium enhancement of the femoral and acetabular lesions previously described, as well as foci with similar signal characteristics and patterns of enhancement in the left superior portion of the sacrum (8 mm), the superior portion of the left sacroiliac joint (6 mm), the inferior portion of the left sacroiliac joint (6 mm), and the anterior portion of the left ilium (7 mm). Periosteal reaction was noted in association with these lesions, and the femoral cortices were thickened but intact. No associated soft tissue masses were seen.

Fig. 2 Whole-body Tc99m-methylene-diphosphonate scintigraphy demonstrates mildly increased tracer uptake in the left proximal femur (A) and diaphysis (B), right proximal femur (C), and anterior left eighth rib (D).

Differential Diagnosis

- Multifocal Langerhans cell histiocytosis
- Hematolymphatic malignancy (leukemia, malignant lymphoma)
- Multifocal Ewing's sarcoma
- Chronic recurrent multifocal osteomyelitis
- Rosai-Dorfman disease
- Camurati-Engelmann disease
- Epithelioid hemangioma of bone

Fig. 3A–D MRI scan of the pelvis and bilateral femora was performed with and without gadolinium contrast. (A) Low T1 signal intensity lesions are apparent in the right superior acetabulum and the proximal femora bilaterally. (B) A small, distinct lesion with low T1 signal intensity is seen in the distal diaphysis of the left femur. (C, D) Right acetabular and bilateral femoral lesions enhanced with gadolinium contrast on T1 sequences with fat saturation demonstrated high T2 signal intensity. Additional foci (not shown) with similar T1/T2 signal characteristics and patterns of enhancement were identified in the left superior portion of the sacrum (8 mm), the anterior portion of the left ilium (7 mm), and the inferior portion of the left sacroiliac joint (6 mm).

A CT-guided core needle biopsy of the right acetabular lesion was performed (Fig. 4), as well as interphase fluorescence in situ hybridization (FISH) analysis (Fig. 5).

Based on the history, physical findings, imaging studies, and histologic picture, what is the diagnosis and how should this patient be treated?

Histology Interpretation

Sections of the core biopsy from the right acetabular lesion demonstrated cortical necrosis and a small round blue cell malignant neoplasm composed of uniform oval cells with “salt and pepper” chromatin and scant cytoplasm (Fig. 4A). Immunohistochemical staining with CD99 revealed a strongly positive, membranous pattern in all cells (Fig. 4B); leukocyte common antigen and cytokeratin immunohistochemistry were negative. TdT and myogenin staining were

negative. Interphase FISH analysis was performed with a breakpoint probe for the EWS gene locus at 22q12 (Fig. 5), and this demonstrated separation of red and green signals indicating the presence of a translocation.

Diagnosis

Multifocal Ewing’s sarcoma

Discussion and Treatment

The clinical presentation of an 18-year-old man with progressive bilateral hip and knee pain associated with intractable night pain is concerning because of the possibility of an infectious or neoplastic process. When the radiographic presentation of a multifocal, polyostotic lytic process is considered in this clinical context, the differential

Fig. 4A–B (A) A section from a core biopsy specimen (right acetabulum) shows a “small blue cell” tumor with few other features of specific differentiation evident (Stain, hematoxylin and eosin;

original magnification, $\times 400$). (B) Immunohistochemical stain for CD99 demonstrates strong positive staining (brown reaction product) in a membranous pattern (original magnification, $\times 400$).

Fig. 5 Interphase FISH with a breakpoint probe for sequences flanking the EWS gene locus at 22q12 reveals separation of red and green signals (arrows), indicating the presence of a translocation.

diagnosis includes multifocal Langerhans cell histiocytosis, leukemia, malignant lymphoma, multifocal Ewing’s sarcoma, chronic recurrent multifocal osteomyelitis, Rosai-Dorfman disease, Camurati-Engelmann disease, and epithelioid hemangioma of bone.

Langerhans cell histiocytosis is characterized by idiopathic proliferation of histiocytes, producing focal or systemic manifestations. Late-stage eosinophilic granuloma, a variant of Langerhans cell histiocytosis, may be considered in a young adult with well-defined osseous

lesions (ie, sclerotic margins and evidence of remodeling) and no evidence of extraskelatal involvement [28].

Hematolymphatic malignancies, such as leukemia and malignant lymphoma, may be associated with diffuse osteolysis and increased radiotracer uptake on whole-body bone scan but are typically associated with pronounced systemic symptoms and laboratory abnormalities.

Ewing’s sarcoma, although rarely multifocal at the time of diagnosis, is the second most common primary bone tumor in children and adolescents and has a predilection for the pelvis and lower extremities [15]. Primary multifocal disease has been observed in 4% to 16% of all patients diagnosed with Ewing’s sarcoma [10, 21, 27].

Chronic recurrent multifocal osteomyelitis may mimic any of the aforementioned conditions. The clinical presentation typically includes localized pain, accompanied by swelling in the affected region [9]. The radiographic appearance may vary from sclerosis to mixed lysis/sclerosis with expansion to bony destruction with collapse; bone scintigraphy reveals multiple asymptomatic foci of activity [9].

Sinus histiocytosis with massive lymphadenopathy, or Rosai-Dorfman disease, is an uncommon benign proliferation of hematopoietic and fibrous tissue that commonly presents with bilateral cervical lymphadenopathy but may rarely present with extranodal disease including multifocal osseous involvement [12, 13, 29].

Camurati-Engelmann disease, also known as progressive diaphyseal dysplasia, is a rare autosomal dominant disorder of intramembranous ossification [4, 30]. The pathophysiology of this disease process is based in aberrant endosteal and periosteal bone formation, producing hyperostosis of the cranial and tubular bones [4]. These patients may present with increased fatigability (due to narrowing of the medullary cavity), as well as leg pain and a waddling gait (due to sclerotic expansion of diaphyseal segments), in the setting of normal laboratory studies [4]. The definitive diagnosis is made on the basis of

radiographic findings: fusiform cortical thickening in the diaphyseal portions of tubular bones, occurring in a symmetrical distribution [30]. Although sporadic cases have been described, patients usually have a positive family history.

Epithelioid hemangiomas of bone are benign vascular tumors, most commonly diagnosed in the fifth decade of life (range, 24–76 years) [25]. Although multifocal involvement has been reported in 8% of cases, the majority of patients present with localized pain [25]. The radiographic features of epithelioid hemangioma may include a lytic or mixed lytic-sclerotic appearance with variable degrees of margination, intralesional bone formation, cortical destruction, and extraosseous extension [25]. Positive immunohistochemical staining for cytokeratin is characteristic [25].

The biopsy findings in this case showed a small round blue cell malignancy, such as metastatic neuroblastoma, leukemia, rhabdomyosarcoma, Ewing's sarcoma, or lymphoma. Although subtle differences among these tumors can be seen on hematoxylin and eosin stained sections, immunohistochemical stains are now commonly used to help achieve a definitive diagnosis. CD99 expression is usually strongly and diffusely positive in Ewing's sarcoma [15] but can also be positive in lymphoblastic lymphoma. Leukemia/lymphoma can be excluded by negative stains for CD45RB and TdT. Although unlikely to present with bone metastases, rhabdomyosarcoma can be excluded by negative immunostaining for myogenin [15]. The diagnosis of Ewing's sarcoma was confirmed by interphase FISH analysis, which was positive for the EWSR1 gene (22q12 translocation). These findings, taken in consideration with the patient's age, obviated the need for synaptophysin staining to rule out neuroblastoma [15].

After definitive diagnosis, additional staging procedures demonstrated no pulmonary, hepatic, or other visceral metastases (Fig. 6). The patient was started on intensive chemotherapy with five cycles of alternating vincristine/adriamycin/cyclophosphamide and ifosfamide/etoposide on a 2-week interval compression schedule and on anti-angiogenic therapy with celecoxib. The chemotherapy was complicated by moderate unilateral sensorineural hearing loss, as evidenced by absence of otoacoustic emissions above 3000 Hz on the right side. After the induction of complete remission, the patient underwent myeloablative therapy with melphalan and total-body irradiation with subsequent autologous stem cell transplantation. After resolution of moderate mucositis, neutropenic fever, and epistaxis, the patient had *Escherichia coli* sepsis develop from a venous access device and was maintained on a 10-day course of home intravenous antibiotic therapy with piperacillin-tazobactam. Restaging with a regional body positron emission tomography (PET) scan was performed

Fig. 6 An 18F-FDG-PET scan with adjunct CT scan for localization of uptake was obtained during initial staging. Intense foci of increased uptake are seen in the L3 vertebral body and bilateral femora. Mildly increased uptake is noted in the superior right acetabulum. Levels of renal and cardiac uptake were within normal physiologic limits; no visceral metastases are apparent.

15 months after the initial diagnosis. The PET scan demonstrated mild nonspecific intramedullary uptake in both proximal and middle femurs and a more discrete focus of mild uptake in the distal left femur; this low-intensity uptake was not thought to represent residual disease. At the time of this report, 19 months after diagnosis, the patient remains in complete remission and denies lower extremity discomfort.

The diagnosis of primary multifocal Ewing's sarcoma is based on specific radiographic and histologic criteria: (1) radiographic evidence of polyostotic disease at initial presentation, with multiple tumor foci evident on plain radiographs, CT, Tc99 m-methylene-diphosphonate scintigraphy, and/or partial- or whole-body MRI; and (2) histopathologic confirmation of Ewing's sarcoma (ie, small round blue cells with strongly positive membranous immunostaining for CD99/MIC-2 and negative staining for TdT, myogenin/Myo-D1, and synaptophysin) [5, 15].

Among patients diagnosed with Ewing's sarcoma, the reported incidence of primary multifocal disease is 4% to 16% [10, 21, 27]. This rate has increased with the implementation of whole-body MRI with short tau inversion recovery (STIR) sequencing and 18F-fluorodeoxyglucose

(FDG) PET in staging. These modalities offer the potential for detection of disease before the onset of metabolic or structural changes in bone. Technetium phosphate-based scintigraphy has proven less sensitive in detection of osseous lesions (sensitivity of 49% to 71% versus 82% to 86% for whole-body STIR-MRI and 90% for 18F-FDG PET); scintigraphy detects the osteoblastic host reaction at a relatively advanced stage of tumor infiltration [11, 22]. A recent comparison of whole-body STIR-MRI to bone scintigraphy in children with suspected multifocal skeletal lesions (including five patients with known or suspected multifocal Ewing's sarcoma) revealed 58% of lesions were evident on STIR-MRI only [22]. Many of the lesions in the pelvis, lower legs, ribs, and upper arms were not observed on bone scintigraphy [22]. Thus, the recent apparent increase in primary multifocal Ewing's sarcoma is likely a reflection of improved detection.

Although multiple series of patients with Ewing's sarcoma have been presented in the literature, few have provided characterization of primary multifocal disease. A recent case series included detailed information on 17 patients with this condition, and results extracted from these data offer valuable insights [8]. The average age at diagnosis was 15.6 ± 4.9 years (SD) (range, 9–31 years). The distribution of osseous lesions included the pelvis (65%), bone marrow (59%), femur (47%), rib (47%), spinal column (47%, with involvement of the lumbar vertebrae in 29% and the sacrum in 12%), tibia (35%), humerus (35%), skull (35%), clavicle (14%), fibula (14%), sternum (14%), radius (5%), and talus (5%). All patients in this series were treated with inductive chemotherapy, myeloablative therapy with total-body irradiation, and hematopoietic stem cell transplantation (autologous in 11 patients, allogeneic in six). The average interval from stem cell transplantation to death was 1.1 ± 1.4 years (range, 0.1–4.9 years). At 5-year followup, only two patients (12%) were alive and in complete remission from their primary tumor; one of the survivors, however, required additional chemotherapy for a secondary liposarcoma of the right pelvis. Secondary tumors were diagnosed in two additional patients, both of whom had myelodysplastic syndrome develop and died from septicemia and multiorgan system failure [4, 8].

Primary multifocal Ewing's sarcoma has been associated with an unfavorable prognosis, as evidenced by a 2-year event-free survival of 15% to 31% [3, 19, 26]. When compared to other patients with advanced Ewing's tumors (ie, those relapsing within 2 years of chemotherapy or suffering multiple relapses), patients with primary multifocal disease treated with contemporary chemotherapy and myeloablative therapy showed a trend toward lower rates of event-free survival at 5 years (0% to 25% versus 24% to 28% for all advanced Ewing's tumors) [5–8, 20, 24, 26]. Relatively advanced age (≥ 17 years) at diagnosis portends

a poor prognosis in some series [5, 8]. Pelvic involvement has not been related to outcome in patients with multiple osseous lesions [8, 21].

In contrast to localized Ewing's sarcoma, primary multifocal disease is not amenable to a multimodal strategy incorporating surgery and conventional radiochemotherapy. In the setting of advanced Ewing's tumors, high-intensity myeloablative therapy has been advocated as a potential therapeutic modality [14]. The rationale for myeloablative therapy draws from the theory that Ewing's sarcoma is a systemic malignancy, derived from multiple independent foci of common neuroectodermal-hematopoietic progenitor cells [5–8, 19]. High-intensity protocols have been advocated as a means of minimizing cumulative chemotherapy dose, secondarily reducing individual risk for development of secondary malignancies [5]. The incorporation of total-body irradiation into the myeloablative regimen has been associated with poorer outcomes (seen with irradiation of greater than 30% of total bone marrow), increased incidence of secondary malignancies, and increased mortality from infection and respiratory complications [7, 26]. Stem cell transplantation has been implemented as an adjunct to high-intensity chemotherapy, and it is required for rescue when greater than 50% of the bone marrow is irradiated; outcomes have been similar between allogeneic and autologous stem cell transplantation [7, 8]. Overall, the results for myeloablative therapy with melphalan have been equivocal in patients with primary multifocal disease [17, 23, 24]. Other therapeutic approaches under investigation include growth factor support, interleukin therapy, and immunotherapy with tumor-specific dendritic cells cultured from CD34+ progenitors [1, 3, 23].

As illustrated in our case report, the clinical presentation of primary multifocal Ewing's sarcoma may be subtle and nonspecific despite the presence of advanced disease. This patient presented only with intermittent bilateral lower extremity pain and a limp; the absence of extremity swelling, palpable masses, systemic symptoms, and laboratory abnormalities would not be anticipated in the context of an advanced Ewing's tumor [2, 10, 15, 16, 18, 27]. The absence of extraskelatal involvement is also surprising, given the extent of polyostotic disease [10, 16, 18, 27]. The potential for subclinical disease underscores the importance of early detection of multifocal involvement (with either whole-body STIR-MRI or 18F-FDG-PET) in patients with suspected Ewing's sarcoma. Prompt implementation of directed chemotherapy, myeloablative therapy, and stem cell transplantation may ameliorate the poor outcomes associated with this challenging clinical entity.

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