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Thigh Pain in a 53-year-Old Woman

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History and Physical Examination

A 53-year-old woman presented with 3 months of progressively worsening right medial thigh pain. She reported having constant severe pain and a burning sensation in the upper thigh. Her pain was worse at night, often awakening her from sleep. Initially, she experienced some relief with aspirin, ibuprofen, and naproxen; however, these no longer provided relief. She obtained partial pain relief with acetaminophen. She had a history of mild, blunt trauma to the left torso approximately 1 month before presentation, but no history of trauma to the affected limb. She denied any back pain, fever, chills, night sweats, or weight loss.

Physical examination revealed a well-developed woman with no obvious deformity. Right antalgic gait was noted. There was no edema, erythema, skin warmth, or palpable mass on examination of the right thigh. Deep palpation did not change her symptoms. There was full and painless active and passive range of motion of the right hip and knee. Neurovascular examination, strength, and tone were normal.

Magnetic resonance images of the right hip and thigh (Fig. 1), CT scans of the right proximal femur (Fig. 2), and a total body bone scan (Fig. 3) were available from the referring physician. Plain radiographs had not been performed at the time of the initial evaluation.

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

Imaging Interpretation

Magnetic resonance images of the right thigh showed a femoral lesion involving the cortex and the medullary canal with a small zone of surrounding medullary and soft tissue edema (Fig. 1). This lesion had low signal intensity on T1-weighted images, high signal intensity on T2-weighted fat-saturated images, and were peripherally enhanced with contrast administration. Computed tomography scans showed involvement of the medial femoral cortex that resembles tunneling without apparent cortical breakthrough (Fig. 2). Delayed Tc-99 bone scan images showed increased uptake in the right medial proximal femur consistent with cortical involvement and a small amount of medullary and left rib involvement (Fig. 3). This is suggestive of focal bone turnover in and around the lesion.

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Each author certifies that his or her institution has approved or waived approval for the reporting of this case, that all investigations were conducted in conformity with ethical principles of research, and that informed consent for participation in the study was obtained.

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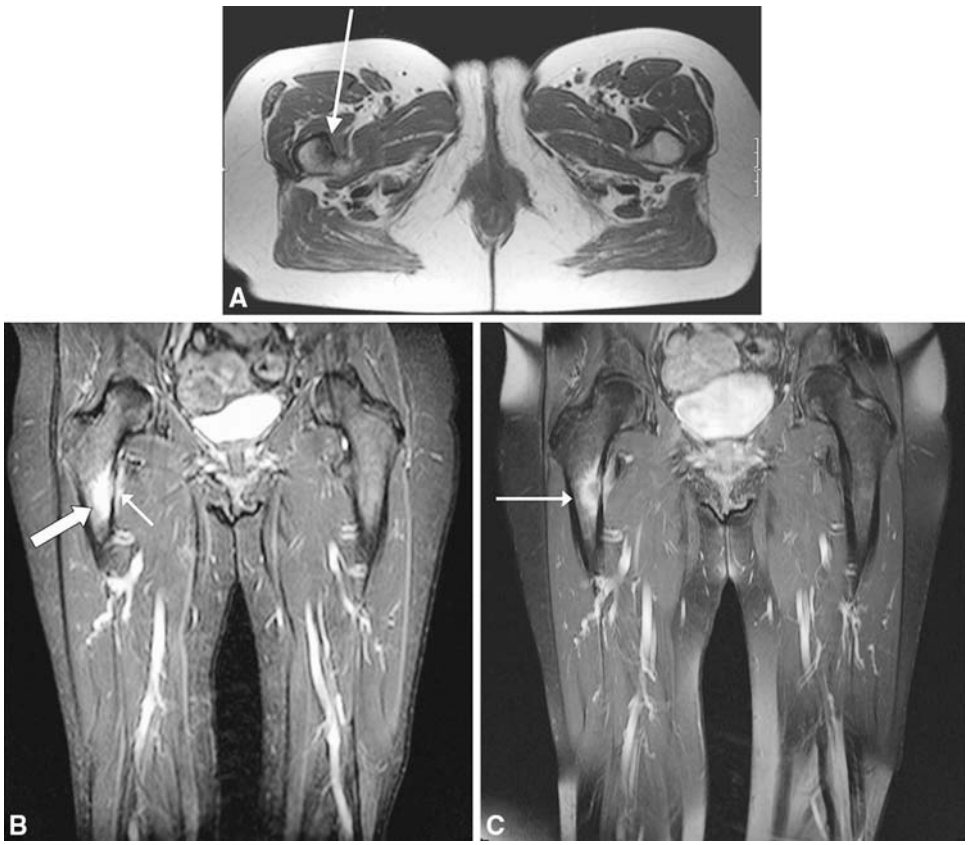

Fig. 1A–C (**A**) An axial T1-weighted MR image shows the low signal of the lesion (arrow) in the femoral canal with involvement of the cortex. (**B**) A coronal T2-weighted fat-saturated MR image shows the hyperintense signal of the lesion (large arrow) with some extraosseous edema (small arrow). (**C**) A coronal, contrast-enhanced, fat-saturated, T1-weighted MR image shows the peripheral enhancement of the lesion (arrow).

Differential Diagnosis

Osteoid osteoma
Metastatic disease
Infection
Eosinophilic granuloma
Lymphoma

A needle biopsy and radiofrequency ablation were performed and the specimen was sent for pathologic examination (Fig. 4). Immunohistochemical staining with CD1a and S-100 also was performed (Fig. 5).

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

Histology Interpretation

On gross examination, the specimens consist of multiple fragments of red core tissue. Scanning magnification showed sheets of cells with eosinophilic cytoplasm, a preponderance of eosinophils, and bone fragments (Fig. 4A). Higher-power magnification showed the cells had eosinophilic cytoplasm with reniform (bean-shaped) nuclei with inconspicuous to small pinpoint nucleoli surrounded by many eosinophils (Fig. 4B). Immunohistochemical stains for CD1a (Fig. 5A) and S-100 (Fig. 5B) highlighted the Langerhans cells.

Diagnosis

Intracortical eosinophilic granuloma

Discussion and Treatment

Eosinophilic granuloma is one manifestation of a spectrum of diseases known as Langerhans cell histiocytosis (LCH). It formerly was known as histiocytosis X and is a rare disorder characterized by clonal proliferation of antigen-presenting mononuclear cells of dendritic origin known as Langerhans cells [20, 22]. This disease was thought to be an immune-mediated reactive disorder until more recently; however, no infectious agent has been isolated. In addition, the clonal proliferation of the Langerhans cells appears to indicate a neoplastic origin [2, 20, 22].

The differential diagnosis for the typical presentation of LCH is broad and includes infection, malignancies such as Ewing sarcoma, lymphoma, or metastasis, and benign lesions such as osteoid osteoma or osteoblastoma [2, 21].

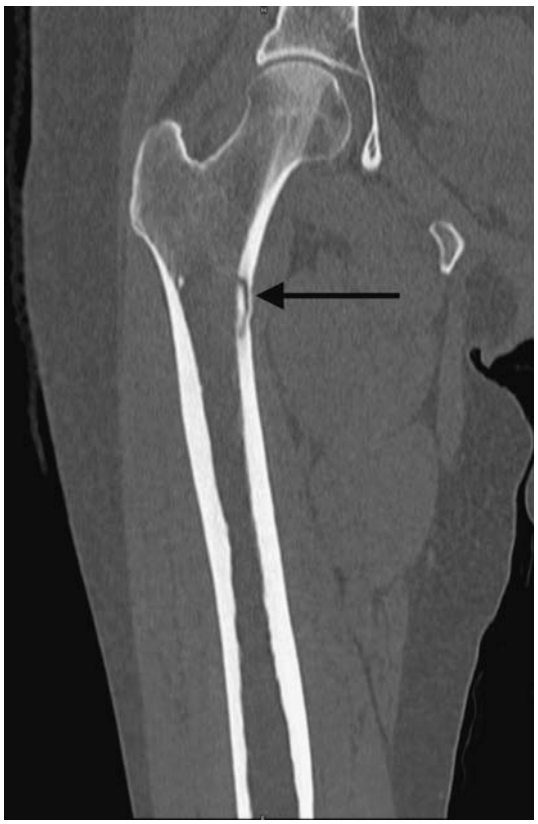

Fig. 2 A coronal CT image shows the medial cortical involvement of the eosinophilic granulomas (arrow).

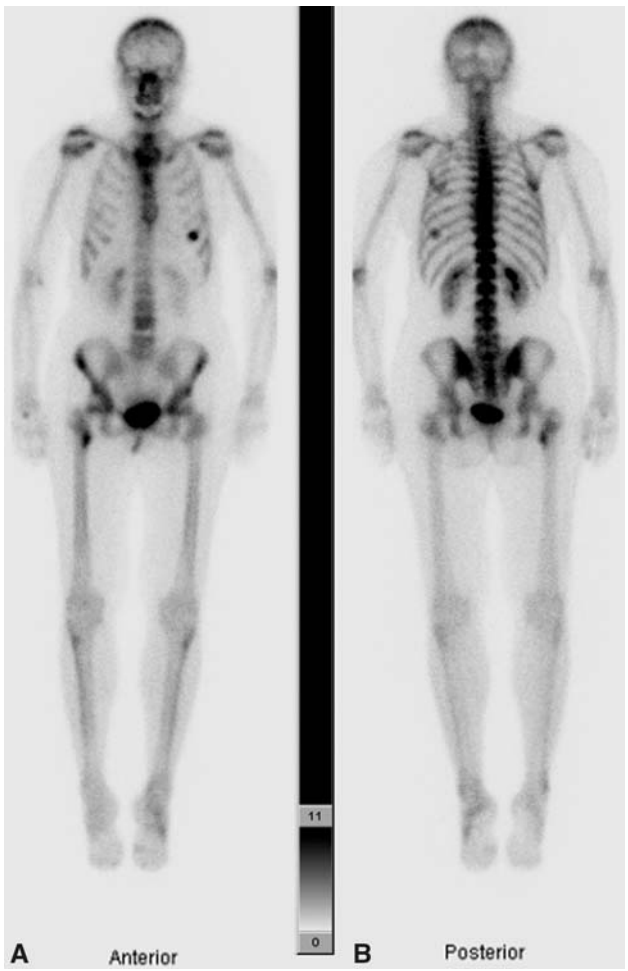

Fig. 3A–B (**A**) Anterior view and (**B**) posterior view delayed Tc-99 bone scan images show increased uptake in the right medial proximal femur at the location of the previously seen lesion, and a focus of uptake in a left rib, which was attributed to the patient's history of trauma (additional workup did not reveal a lesion).

The intracortical long bone lesion presented in this case is atypical for an eosinophilic granuloma [2], so osteoid osteoma, infection, and metastasis were high on our differential before this lesion was definitively diagnosed with biopsy. Like eosinophilic granuloma, osteoid osteoma most frequently occurs in young patients, but it remained high on the differential owing to the size of the lesion and the patient's history of obtaining some relief with NSAIDS. Metastatic disease and lymphoma also can cause substantial pain and are present in this patient's age group. As infection can mimic many diseases of bone, this was on the differential list; however, the surrounding edema present in eosinophilic granuloma is less extensive than the edema seen with infectious processes [5], which is apparent in this case. Although stress fracture should be considered with this patient's history and the benign-appearing surrounding edema, the presence of peripheral enhancement which resembles a lesion made this diagnosis doubtful.

The unifying feature of LCH is the clonal proliferation of Langerhans cells. When this occurs as solitary or multiple bone lesions without systemic involvement, it is known as eosinophilic granuloma. Langerhans cell histiocytosis also may present as extraosseous lesions or with multisystem involvement, which are more commonly found in the pediatric population. The triad of skull lesions, exophthalmos, and diabetes insipidus is referred to as Hand-Schuller-Christian disease. Letterer-Siwe disease is an aggressive, multifocal, systemic, and often fatal form of LCH that usually presents in infancy. These three clinical entities are thought to be different manifestations of the same underlying proliferative process [8].

The typical presentation of LCH is recent onset of pain with or without swelling in the area of a solitary bone lesion [4, 11–13]. Subcutaneous edema also may be visible if the lesion is in a bone with little soft tissue coverage, such as the clavicle [4]. Pathologic fracture complicates approximately 16% of cases [12]. Langerhans cell histiocytosis most commonly presents in the pediatric population, with the majority of cases occurring during the first 5 years of life [7, 13]. However, it can manifest at any age, and some reports suggest 30% to 40% of cases occur

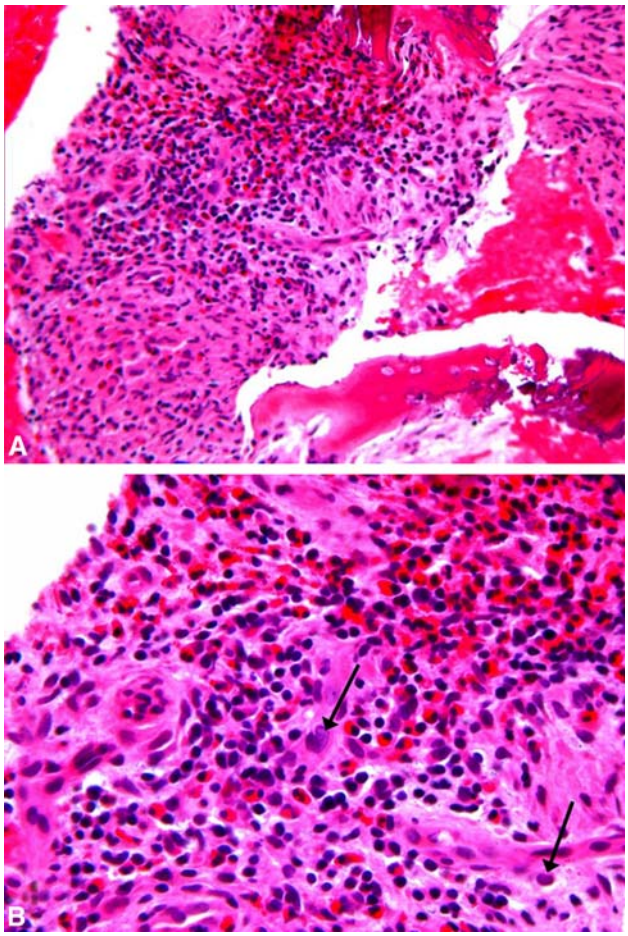

Fig. 4A–B (**A**) A low-power view shows sheets of cells with eosinophilic cytoplasm admixed with a preponderance of eosinophils (Stain, hematoxylin and eosin; original magnification, ×10). (**B**) A medium-power view shows the Langerhans cells with reniform or bean-shaped nuclei (arrows) and inconspicuous to small nucleoli in an inflammatory soup of eosinophils (Stain, hematoxylin and eosin; original magnification, ×20).

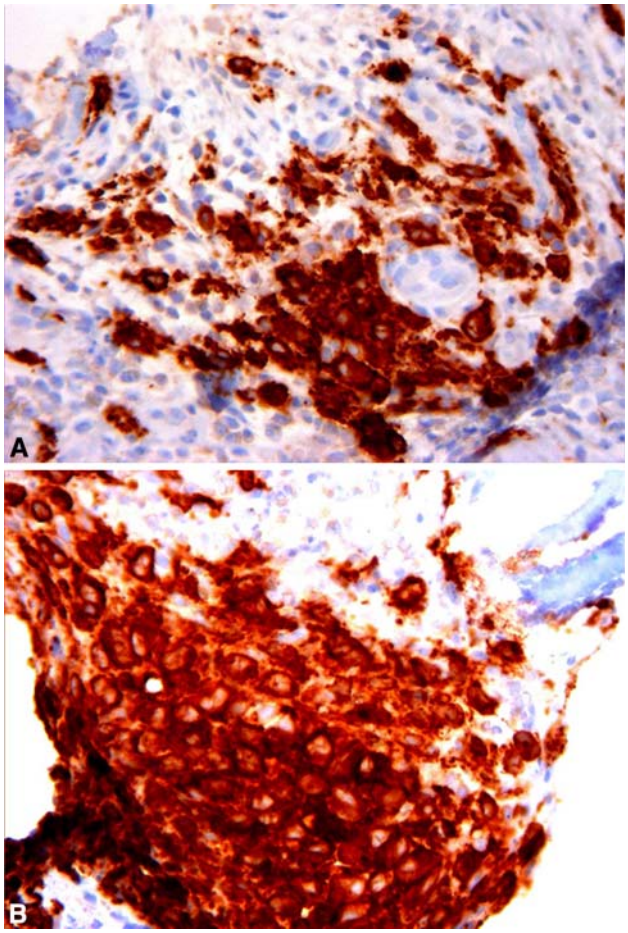

Fig. 5A–B (**A**) CD1a immunohistochemical stain highlights the Langerhans cells (Original magnification, ×40). (**B**) S-100 immunohistochemical stain decorates the Langerhans cells (Original magnification, ×40).

in adults [12–14]. In adults, extraosseous involvement occurs in approximately 10% of cases, with eosinophilic granuloma of the lung being the most common extraosseous manifestation.

Langerhans cell histiocytosis can affect any bone in the body; however, bone lesions are most common in the axial skeleton, such as the skull, ribs, vertebrae, and mandible [6, 12, 13]. The appendicular skeleton is involved ⅓ of the time [2], with the femur, humerus, and clavicle being the most frequent sites [12]. Lesions are diaphyseal in the majority of appendicular cases, with most of the remaining lesions being metaphyseal [12]. Epiphyseal lesions are reported to be rare in children [12].

Imaging typically begins with plain radiographs, although our patient did not get preprocedure radiographs. The radiographic appearance of a lesion is variable and will depend on location and the stage of the lesion. Acute or active lesions typically have an osteolytic appearance with poorly defined margins without surrounding sclerosis [2, 13, 19]. An active lesion in a long bone often will cause medullary destruction, which may progress to endosteal scalloping, cortical erosion, or periosteal reaction [4, 5, 12]. The periosteal reaction can be multilayered (laminated) [2, 13], which may resemble the onion skin periosteal reaction of Ewing's sarcoma. These nonspecific radiographic characteristics often make active lesions difficult to differentiate from tumor or infection [16]. In the spine, vertebral body lesions are the most common location often characterized by anterior wedging or near-total collapse (known as vertebra plana) with disc-space preservation [9]. Chronic lesions can have well-defined borders and reactive sclerosis [2].

As LCH can involve multiple sites, it is important to screen for other lesions. There is some debate regarding whether radionuclide skeletal scintigraphy or radiographic skeletal survey is more sensitive. Lesions that have been

treated with chemotherapy or are not active may not be detected with a bone scan, whereas very small actively growing lesions likely will be visible on a bone scan before being visible on radiographs. Additionally, sensitivity may be affected by the anatomic site, as lesions of the ribs, spine, and pelvis are more likely missed with radiography than with a bone scan [6].Therefore, some authors suggest both modalities be used, as they may provide complimentary information [6, 17].

Computed tomography and MRI, although quite sensitive, are not specific enough to preclude biopsy [11]. Their roles are limited to helping define the extent of the lesion and planning for biopsy. Computed tomography will provide excellent detail of bony involvement (Fig. 2). With MRI, osteolytic lesions are typically hypointense on T1 and hyperintense on T2 and STIR (Fig. 1) [2, 5, 11, 16]. Significant gadolinium enhancement is common in bone lesions [2], and rim enhancement has been reported [16]. In addition, MRI shows the extent of edema caused by the lesions better than plain radiography or CT [5, 16]. Magnetic resonance imaging also is useful in better defining the intramedullary and extraosseous extent of the tumor [5], and may prove useful in the spine, as it can depict preservation of disc spaces, which can aid in differentiation from infection [2]. Although there is limited experience using PET in diagnosis of LCH, early findings indicate PET may be more sensitive and may predict response to treatment earlier than radiographs or a bone scan, but additional investigation is necessary [3].

Histologically, the bone lesions have sheets of cells with eosinophilic cytoplasm, a preponderance of eosinophils, and bone fragments. Higher magnification reveals large, elongated Langerhans cells with abundant eosinophilic cytoplasm and a bean-shaped nucleus (Fig. 4) [2, 13]. The nuclei have vesicular chromatin with inconspicuous to small pinpoint nucleoli. Formerly, electron microscopy showing Birbeck granules was used to confirm the diagnosis, but today immunohistochemical staining for CD-1a and S-100 can highlight the Langerhans cells (Fig. 5) [2, 8, 10].

Langerhans cell histiocytosis has a variable and unpredictable prognosis. Disease localized to one site often has a benign course and even may spontaneously regress [2, 11]. However, multisystem disease has a 10% to 20% mortality rate [1]. Ambiguity about the pathogenesis of LCH and variability of treatment outcomes have prevented the development of a standardized treatment protocol [1]. Treatment often is individualized based on symptoms, morbidity, extent of disease, and location of the lesion(s). Mild isolated bone lesions can be observed and may spontaneously heal [2, 11]. Lesions that are symptomatic, few, and accessible may be treated with intralesional injection of corticosteroid or surgical curettage with grafting [2, 21]. Yasko et al. reported an 89% resolution rate after one percutaneous injection of corticosteroid [1], and Schreuder et al. reported successful treatment of six lesions combining cryotherapy with curettage and bone grafting, although one patient had a subsequent pathologic fracture [18].

Radiation therapy is also an option, especially for lesions for which surgical morbidity would be high, as local control rates greater than 90% have been reported for low-dose radiation therapy in isolated bone lesions [15]. For cases with numerous bone lesions, multisystem involvement, or involvement of facial bones, chemotherapy with agents such as vinblastine, steroids, methotrexate, cyclophosphamide, and etoposide are effective, although they all have relatively high rates of side effects or complications [1, 11]. Despite these therapeutic options, as much as 20% of patients with multisystem disease will not respond to treatment and will have a high mortality rate [2].

We performed radiofrequency ablation of the lesion in our patient because we believed the lesion was an osteoid osteoma and because the location of the lesion made it easily accessible for a minimally invasive percutaneous procedure. The patient subsequently had an increase in pain, which progressively decreased during the next 6 weeks while she was on crutches. She was pain-free 12 weeks posttreatment, with plain radiographs showing continued involvement of the medial femoral cortex without cortical breakthrough (Fig. 6). The left rib lesion

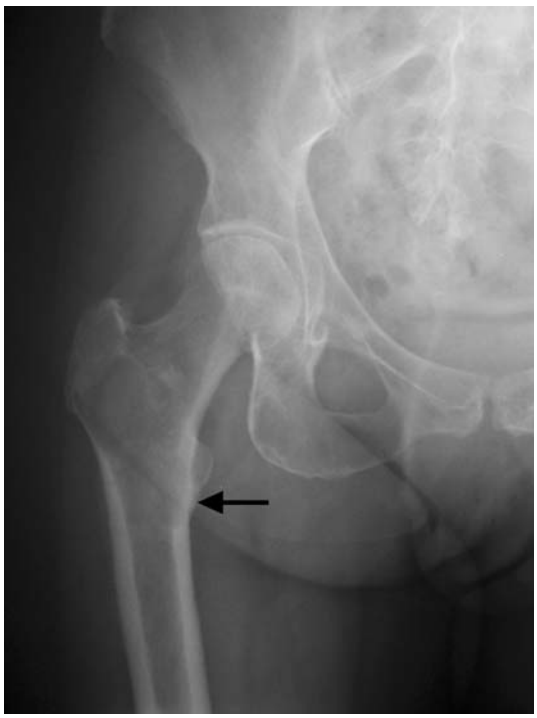

Fig. 6 A plain anteroposterior radiograph of the right hip shows the presence of a small cortical defect on the medial cortex of the femur near the lesser trochanter (arrow).

that had increased uptake on the bone scan was attributed to previous trauma after additional workup was negative. At her most recent followup 15 months after radiofrequency ablation, she had no pain in her right thigh and walked normally without assistance. We could not find any articles in the English literature describing the use of radiofrequency ablation for treatment of eosinophilic granuloma. Our patient had successful treatment of one eosinophilic granuloma lesion with radiofrequency ablation with improvement of symptoms and partial healing of the lesion. This case underscores the importance of forming a differential diagnosis and completing a thorough workup because a rare case occasionally will contradict our initial impression.

References

1. Arico M. Langerhans cell histiocytosis in adults: more questions than answers?. *Eur J Cancer*. 2004;40:1467–1473.
2. Azouz EM, Saigal G, Rodriguez MM, Podda A. Langerhans' cell histiocytosis: pathology, imaging and treatment of skeletal involvement. *Pediatr Radiol*. 2005;35:103–115.
3. Binkovitz LA, Olshefski RS, Adler BH. Coincidence FDG-PET in the evaluation of Langerhans' cell histiocytosis: preliminary findings. *Pediatr Radiol*. 2003;33:598–602.
4. Bunch WH. Orthopedic and rehabilitation aspects of eosinophilic granuloma. *Am J Pediatr Hematol Oncol*. 1981;3:151–156.
5. Davies AM, Pikoulas C, Griffith J. MRI of eosinophilic granuloma. *Eur J Radiol*. 1994;18:205–209.
6. Dogan AS, Conway JJ, Miller JH, Grier D, Bhattathiry MM, Mitchell CS. Detection of bone lesions in Langerhans cell histiocytosis: complementary roles of scintigraphy and conventional radiography. *J Pediatr Hematol Oncol*. 1996;18:51–58.
7. Egeler RM, D'Angio GJ. Langerhans cell histiocytosis. *J Pediatr*. 1995;127:1–11.
8. Favara BE, Feller AC, Pauli M, Jaffe ES, Weiss LM, Arico M, Bucsky P, Egeler RM, Elinder G, Gadner H, Gresik M, Henter JI, Imashuku S, Janka-Schaub G, Jaffe R, Ladisch S, Nezelof C, Pritchard J. Contemporary classification of histiocytic disorders. The WHO Committee On Histiocytic/Reticulum Cell Proliferations. Reclassification Working Group of the Histiocyte Society. *Med Pediatr Oncol*. 1997;29:157–166.
9. Garg S, Mehta S, Dormans JP. Langerhans cell histiocytosis of the spine in children: long-term follow-up. *J Bone Joint Surg Am*. 2004;86:1740–1750.
10. Geevasinga N, Jeremy R, Crombie CM, Manolios N. Histiocytosis and bone: experience from one major Sydney teaching hospital. *Intern Med J*. 2005;35:622–625.
11. Ghanem I, Tolo VT, D'Ambra P, Malogalowkin MH. Langerhans cell histiocytosis of bone in children and adolescents. *J Pediatr Orthop*. 2003;23:124–130.
12. Islinger RB, Kuklo TR, Owens BD, Horan PJ, Choma TJ, Murphey MD, Temple HT. Langerhans' cell histiocytosis in patients older than 21 years. *Clin Orthop Relat Res*. 2000;379:231–235.
13. Kilpatrick SE, Wenger DE, Gilchrist GS, Shives TC, Wollan PC, Unni KK. Langerhans' cell histiocytosis (histiocytosis X) of bone: a clinicopathologic analysis of 263 pediatric and adult cases. *Cancer*. 1995;76:2471–2484.
14. Lieberman PH, Jones CR, Steinman RM, Erlandson RA, Smith J, Gee T, Huvos A, Garin-Chesa P, Filippa DA, Urmacher C, Gangi MD, Sperber M. Langerhans cell (eosinophilic) granulomatosis: a clinicopathologic study encompassing 50 years. *Am J Surg Pathol*. 1996;20:519–552.
15. Olschewski T, Seegenschmiedt MH. Radiotherapy of Langerhans' cell histiocytosis: results and implications of a national patterns-of-care study. *Strahlenther Onkol*. 2006;182:629–634.
16. Pavlik M, Bloom DA, Ozgonenel B, Sarnaik SA. Defining the role of magnetic resonance imaging in unifocal bone lesions of langerhans cell histiocytosis. *J Pediatr Hematol Oncol*. 2005;27:432–435.
17. Schaub T, Ash JM, Gilday DL. Radionuclide imaging in histiocytosis X. *Pediatr Radiol*. 1987;17:397–404.
18. Schreuder HW, Pruszczynski M, Lemmens JA, Veth RP. Eosinophilic granuloma of bone: results of treatment with curettage, cryosurgery, and bone grafting. *J Pediatr Orthop B*. 1998;7:253–256.
19. Stull MA, Kransdorf MJ, Devaney KO. Langerhans cell histiocytosis of bone. *Radiographics*. 1992;12:801–823.
20. Willman CL, Busque L, Griffith BB, Favara BE, McClain KL, Duncan MH, Gilliland DG. Langerhans'-cell histiocytosis (histiocytosis X): a clonal proliferative disease. *N Engl J Med*. 1994;331:154–160.
21. Yasko AW, Fanning CV, Ayala AG, Carrasco CH, Murray JA. Percutaneous techniques for the diagnosis and treatment of localized Langerhans-cell histiocytosis (eosinophilic granuloma of bone). *J Bone Joint Surg Am*. 1998;80:219–228.
22. Yu RC, Chu C, Buluwela L, Chu AC. Clonal proliferation of Langerhans cells in Langerhans cell histiocytosis. *Lancet*. 1994;343:767–768.