Langerhans cell histiocytosis with multiple spinal involvement

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Received: 5 April 2009 / Revised: 31 October 2009 / Accepted: 9 March 2010 / Published online: 22 May 2010
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Abstract To stress the clinical and radiologic presentation and treatment outcome of Langerhans cell histiocytosis (LCH) with multiple spinal involvements. A total of 42 cases with spinal LCH were reviewed in our hospital and 5 had multifocal spinal lesions. Multiple spinal LCH has been reported in 50 cases in the literature. All cases including ours were analyzed concerning age, sex, clinical and radiologic presentation, therapy and outcome. Of our five cases, three had neurological symptom, four soft tissue involvement and three had posterior arch extension. Compiling data from the eight largest case series of the spinal LCH reveals that 27.2% multiple vertebrae lesions. In these 55 cases, there were 26 female and 29 male with the mean age of 7.4 years (range 0.2–37). A total of 182 vertebrae were involved including 28.0% in the cervical spine, 47.8% in thoracic and 24.2% in the lumbar spine. Extraspinal LCH lesion was documented in 54.2% cases, visceral involvement in 31.1% and vertebra plana in 50% cases. Paravertebral and epidural extension were not documented in most cases. Pathological diagnosis was achieved in 47 cases including 8 open spine biopsy. The treatment strategy varied depending on different hospitals. One patient died, two had recurrence and the others had no evidence of the disease with an average of 7.2 years (range 1–21) of follow-up. Asymptomatic spinal lesions could be simply observed with or without bracing and chemotherapy

is justified for multiple lesions. Surgical decompression should be reserved for the uncommon cases in which neurologic compromise does not respond to radiotherapy or progresses too rapidly for radiotherapy.

Keywords Langerhans cell histiocytosis · Spine · Multifocal disease · Biopsy · Treatment

Introduction

Langerhans cell histiocytosis (LCH) is a rare condition distinguished by a clonal proliferation and accumulation of a specific histiocyte: the Langerhans cell [2, 17, 18]. LCH is manifested either as localized (unifocal or multifocal) or systemic. Clinical variants of LCH include eosinophilic granuloma (EG, the most benign variant that primarily affects children and young adults, either single or multifocal bone lesion without visceral involvement), Hand–Schüller–Christian disease (typically in children with classic triad of skull lesions, exophthalmos and diabetes insipidus) and Letterer–Siwe disease (life-threatening, disseminated lesions involving visceral organs which presents during infancy or early childhood) [19].

The incidence of vertebral involvement varies between 6.5 and 25% of all skeletal LCH cases and it is generally a solitary lesion [4, 22]. Multiple spinal LCH, including multifocal spinal lesions (lesions in two or more separated vertebrae) and/or solitary lesions (one lesion involving several consecutive vertebrae), is even rarely reported [33]. As a result of the low frequency with which spine lesions are encountered in clinical practice, there are few studies in the literature focusing on this specific disease. The diagnosis and treatment protocols for spine LCH are still controversial and problematical for its rarity [17].

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A search of the MEDLINE databank located 13 studies and totally 50 cases of LCH with multiple spinal lesions [1, 3, 5, 11, 13, 20, 21, 23, 26, 27, 32–35]. We reported five additional cases and a meta-analysis of all cases was also performed.

Materials and methods

We only collected the cases diagnosed in the past 10 years. Because our patients' addresses and telephone numbers changed frequently with the substantive city renovation in China, we lost the follow-up of most of the cases before 1997. A retrospective review of the hospital charts, OR reports, office charts and radiographs were performed. Data collected included patient age, gender, radiological features, pathology, treatment and outcome.

Image

We routinely took anteroposterior and lateral spine roentgenograms, skeletal radiographic surveys and/or technetium bone scan, computed tomography (CT) and magnetic resonance image (MRI). We took roentgenograms at 3, 6 and 12-month follow-up and annually thereafter. CT reconstruction was taken at 3-month follow-up. MRI was ordered if the lesion had the paravertebral or epidural extension. At the final follow-up, CT was also ordered to evaluate the bony reconstruction.

Biopsy

We tried to achieve the pathological diagnosis for each suspected LCH case. We also tried to avoid open biopsy for the possible vertebral growth plate damage. If there were multiple lesions, the most accessible lesion was appropriate for biopsy. Otherwise, specimen was obtained by percutaneous CT guided needle biopsy from the most accessible spinal lesion.

Treatment protocol

Immobilization was always the first choice. For those cases with solitary spinal lesion with marked bony erosion (even with paravertebral soft tissue extension), radiotherapy was suggested. For those cases with separated multifocal lesions, chemotherapy was suggested. Additional local radiotherapy was also suggested for severe bony destruction. Surgical treatments were preserved for specific cases involving suspected malignancy, neurologic defects, severe deformity or instability.

Results

From October 1997 to December 2006, 42 consecutive patients with spinal LCH were diagnosed in our department. Only five (11.9%) had spine lesions involving multiple vertebrae including 3 cases with consecutive lesions, 1 with separated lesions and 1 with combined (both consecutive and separated) lesions.

This series included four male and one female, and the mean age at diagnosis was 18 years (range 12–23). All the patients had back or neck pain and three cases had neurological symptoms. A total of 19 vertebrae were involved without visceral lesion (including 5 cervical, 12 thoracic and 2 lumbar–sacral vertebrae). Vertebra plana was only observed in three vertebrae (3/19, 15.8%). Paravertebral soft tissue extension was observed in four cases, epidural extension in three and posterior arch (pedicle and/or lamina) extension in three cases. All the cases had pathological diagnosis, three by vertebral needle biopsy under CT guidance and two by operation. One had recurrence due to incomplete treatment and the others had no evidence of disease during the average 78.6 months (range 36–170) follow-up.

Case 1

A 23-year-old lady presented with a 2-week history of low back pain. The pain was more severe in the left side at night. The tenderness was in her left iliosacral joint. Her erythrocyte sedimentation rate (ESR) was 61 cm/h. Bone scan revealed intense osteoblastic lesion at atlantoaxial spine, L3, left iliosacral joint, left humerus and left scapula. CT and MRI showed osteolytic lesion at S1 and L3 with epidural and paravertebral extension. Percutaneous needle biopsy of the S1 lesion under CT guidance stained positive for CD-1a and S-100. A diagnosis of LCH was made according to Histiocyte Society guidelines [9]. The patient had chemotherapy (cyclophosphamide, doxorubicin, vincristine and prednisone) and local radiotherapy. One month later, her pain completely resolved. She remained free of symptoms without disease recurrence at the 36-month follow-up.

Case 2

A 14-year-old boy presented with a 6-month history of intermittent back pain and stiffness. His ESR was 15 cm/h. CT and MRI revealed T11 vertebral plana, irregular T10 with slight regional kyphosis (Fig. 1a–d) and lamina extension (Fig. 1e, f). Bone scan confirmed this was a solitary lesion. Percutaneous needle biopsy confirmed the diagnosis of LCH. The spine was considered stable and surgical intervention seemed unnecessary. The patient had immobilization and radiotherapy. One month after

Fig. 1 Radiography showed T11 vertebral plana and irregular T10 with slight regional kyphosis (**a**, **b**). MRI revealed that the lesion extended to the right neural foramen of T10 (**c**, **d**). Axial CT manifested that the osteolytic lesion extended from vertebral body to

the lamina of T10 (**e**, **f**). At the 8 (**g**) and 57-month follow-up (**h–k**), the lytic lesion healed and the shape of collapsed vertebral bodies did not change with slight regional kyphosis

radiotherapy his symptoms completely resolved. The shape of collapsed vertebrae did not change at 57-month follow-up (Fig. 1**h–k**). The patient had no discomfort during his daily activity.

Case 3

A 22-year-old man had neck pain for 2 years. The pain was exaggerated in the past 20 days with left arm weakness

(muscle power Grade 4/5). His ESR was 41 mm/hr. CT and MRI manifested C4–6 vertebral body bony destruction with paravertebral and epidural extension (Fig. 2**a–e**), which led to the suspected diagnosis of tuberculosis (TB). The patient underwent curettage and reconstruction without preoperative biopsy. The postoperative pathological diagnosis was LCH. From retrospective view, C5 vertebral collapse seemed to be an atypical vertebral plana, and this case should not have been simply diagnosed as TB of the

Fig. 2 CT and MRI manifested C4–6 vertebral body bony destruction with paravertebral and epidural extension (a–e). Lateral radiography and CT reconstruction showed solid fusion with slight kyphosis at the 61-month follow-up (f, g)

intact adjacent endplates and discs. He was symptom free at the 61-month follow-up.

Case 4

A 19-year-old man presented with back pain for 6 months. He had numbness in his bilateral arms and weakness in the right hand and lower extremity for 1 month. He had muscle atrophy in his right forearm and hand. His ESR was 8 mm/h. The huge paravertebral extension seemed quite aggressive with vertebral destruction. The collapsed T1 vertebra extruded posteriorly into the spinal canal. He had right carotid vein thrombosis after admission in the ward. The biopsy pathology was LCH. After radiotherapy (1,980 cGy) his pain resolved, and then he had one stage anterior and posterior tumor excision and reconstruction. There was no recurrence at the 63-month follow-up. From retrospective view, the surgery seemed too aggressive from the appearance on CT and MRI.

Case 5

A 12-year-old boy with back pain was diagnosed with TB in another hospital. He had laminectomy followed by radiotherapy (36 Gy) and the postoperative histological pathology diagnosis was LCH. His back pain was

intermittent in the previous 12 years which exaggerated 2 months ago with weakness of the bilateral lower extremities. He was 24 years old when he was referred to our hospital. He had sinus tract on his back and thoracic kyphosis with a single vertebra plana (Fig. 3b, c, arrow head). The lesion involved T1–7 and T10 vertebrae (Fig. 3d–i, thin arrow) with paravertebral and bilateral ribs extension (thick arrow). The sinus tract was excised and repaired followed by additional intensity-modulated radiotherapy. His weakness of the lower extremities and back pain resolved, and he could return to his work as a peasant. He still had thigh pain, but refused for further treatment for financial reason. His symptoms were unchanged at the 24-month follow-up. He lost all of his previous images, but his parents stated that his deformity developed slightly during the previous 14 years.

Meta-analysis literature review and discussion

A meta-analysis of all cases was performed for the 50 cases found in the MEDLINE databank and our own 5 cases. Sex and age distribution, clinical symptoms, radiologic features, biopsy, treatment and outcome were assessed.

Including our cases, 55 LCH cases with multiple spinal lesions have been reported in the past 40 years. Compiling

Fig. 3 A 24-year-old man presented with a 12-year history of thoracic LCH and laminectomy. Radiography showed thoracic kyphosis (a, b). The lesion involved T1–7 and T10 vertebrae (c–i) with paravertebral and bilateral ribs extension (*thick arrow*)

data from the eight largest case series of the spinal LCH reveals that 49 of 180 cases (27.2%) had multiple vertebrae lesions [3, 5, 11, 13, 20, 23, 26, 27, 35].

Demographics

There were 26 females and 29 males, and the mean age was 7.4 years (range 0.2–37). The mean age was 5.1 years (range 0.2–16) in the 49 children. Twenty-seven (49.1%) cases were below 5 years, 14 (25.5%) between 5 and 10, 8 (14.5%) between 10 and 18 years old. The average age was 25.2 years (range 19–37) in the 6 (11.3%) adult cases. The gender distribution (female-to-male) in children was 1.04:1, whereas 1:5 in adult cases.

Langerhans cell histiocytosis is usually regarded as a pediatric disease. LCH was reported to have a peak incidence between 5 and 10 years of age with male predilection [2, 18]. Recent studies have reported as many as 39% of diagnosed cases in adults [19]. Spine lesion is less common in the adult group (3 vs. 10%) [19]. In this review, half patients were below 5 years, partly because Hand–Schüller–Christian disease and Letterer–Siwe disease are most common in baby patients with more multifocal skeletal involvement.

Nesbit and his colleagues [23] focused on patients below 5 years, therefore, 60% of his patients had visceral involvement and 50% had multiple spinal involvements. Floman et al. [11] focused spinal lesion in elder cases and only 20% had multiple spinal lesions. Since we do not have paediatric orthopedic specialists in our hospital, most of our cases were adolescents or young adults, and only 11.9% had multiple spinal lesions without visceral lesion.

There have been differing reports on gender distribution in LCH. Our review has similar result as Islinger's review [19]. The gender distribution was nearly equal in children, whereas male was predominant in the adult cases.

Location

A total of 182 vertebrae were involved, including 51 (28.0%) in the cervical spine, 87 (47.8%) in thoracic and 44 (24.2%) in the lumbar. In the six adult cases, most lesions were located in the cervical spine (9/14, 64.3%). The spine lesions were intermittent in 30 cases, continuous in 11 and combined in 14.

Extraspinal LCH lesion was documented in 26 (26/48, 54.2%) cases and visceral involvement in 14 (14/45, 31.1%) cases. Paravertebral and epidural extension were not documented in most cases that were diagnosed before the prevalence of CT or MRI.

LCH was reported to be mainly located in the vertebral body, with a predilection for the thoracic spine followed by lumbar and cervical spine [2]. Mammano et al. [22] reported that the thoracic spine was involved in 54% of their cases, whereas 35% occur in the lumbar region and 11% in the cervical spine. In this review of multifocal spinal lesions, thoracic spine lesion was still the most common region (48.9%), and then the cervical (27.5%) and lumbar spine (23.6%). In these 55 cases, the average number of involved vertebrae was 3, but it reaches 10 in one case. Extraskelatal disease was reported in 8–10% cases with spine LCH involvement [13], but it was 31.1% in this meta-analysis (14/45).

Clinical presentation

Pain and neurological symptoms were the presenting symptoms in 33 (33/40, 82.5%) and 8 (8/29, 27.6%) cases, respectively. Vertebra plana was observed in 50% cases (13/26).

Typical presentation of LCH of the spine is dull back pain without neurological involvement which is nonspecific [18]. The classic radiography is vertebra plana without soft tissue mass or posterior arch extension [17, 31]. But the presentation and clinical course could be quite variable. Spinal involvement could be totally asymptomatic [27].

In our five cases with multiple vertebrae involvement, soft tissue mass was revealed in four cases. Both neurological deficit and posterior arch extension were observed in three cases. These results may be attributable in part to our being a tertiary referral center mainly for adult cases. In previous reports, most cases were baby or child without CT and MRI examination, but our cases were adolescent or young adult [13, 19, 23, 27].

A review of the literature shows a wide spectrum of clinical and radiographic presentation. Neurologic symptoms were supposed to be very uncommon. But neurologic symptom was as high as 33% in Bertram's review [4] of 53 cervical LCH cases, and it was 27.6% in this analysis.

Biopsy

In these 55 cases, 47 had pathological diagnosis, including 21 nonspinal lesion biopsy, 14 percutaneous spine lesion biopsy and 8 open spine biopsy. Biopsy failed in two cases and was not clearly documented in two other cases. Biopsy was not done in eight cases (including 5 diagnosed before 1969).

The necessity for vertebral biopsy is still debatable [35]. Some authors suggested that most spine LCH lesions have typical presentation and a vertebral biopsy is usually unnecessary. Yeom et al. [35] believed that close observation with frequent clinical and radiologic examination is more appropriate than vertebral biopsy in patients with typical vertebral lesions, without evidence or suspicion of malignancy. But some other authors preferred biopsy [5, 26].

Currently, clinical clues alone do not identify LCH accurately. There have been numerous case reports of spinal EG without vertebral collapse or vertebra plana [4]. So called "characteristic imaging features" are not sufficient for the diagnosis of LCH. Several pathologic conditions may also cause vertebra plana, such as Ewing sarcoma, osteosarcoma, lymphoma, aseptic necrosis, juvenile osteochondritis, vertebral osteomyelitis, tuberculosis and hemangiomas [24, 29]. Besides, characteristic imaging features are not that common with the prevalence

of CT and/or MRI. Despite an aggressive appearance on MRI, biopsy results confirmed the diagnosis of LCH (Fig. 3). Appropriate histopathological studies are required to establish or rule out the diagnosis of LCH. One of our five cases was misdiagnosed as tuberculosis and surgical treatment might be avoided with the appropriate histopathological diagnosis (case 3).

In the literature review, most cases had pathological diagnosis. We routinely had percutaneous CT guided needle biopsy except typical presentation with multifocal lesions and vertebra plana without posterior arch, epidural or paravertebral extension. The most accessible lesion was the one appropriate for biopsy. Some authors fear that needle biopsy might destroy the growth plate in the case of children. Since the needle is usually inserted in parallel with the endplate, the growth plate could not be damaged during biopsy.

But in cases of severe vertebral collapse, the lesion might be too small for biopsy, or the biopsy specimen might be inadequate to achieve appropriate pathological diagnosis. Sometimes, the pathologists might be confused by the tiny specimen with both bony destruction and reconstruction [34]. In Brown's study [5], the pathological findings were inconclusive in two, and we had a similar experience. Therefore, final diagnosis should be based on the combination of the clinical, radiological and pathological data.

Bone scan

A complete clinical, laboratory and radiologic work-up is also necessary for adequate treatment based on the extent of the LCH [26]. It is recommended that a technetium bone scan or a skeletal survey be performed early during the evaluation of every case with a suspected spinal lesion. Bone scintigraphy is not as sensitive as a skeletal radiograph survey, but the total radiation dose is less in a bone scan than in a skeletal survey [2, 6, 8, 10, 13, 18]. The finding of multiple sites of disease allows the physician to have increased confidence in the diagnosis since other entities that may present with vertebral collapse do not occur at multiple sites. [22] Furthermore, this information can help to determine whether chemotherapy is needed. Although MRI had been used to follow spinal LCH lesions [1], bone scan is important to monitor all sites of disease for progression and pathologic fracture [13].

Treatment and outcome

Immobilization was used in 13 cases, not suggested in 13 and not documented in the other 29 cases. Chemotherapy was carried out in 34 cases, radiotherapy in 22 and surgery in 13. Seven cases were observed without chemotherapy,

radiotherapy or surgery. All the cases except one had an average 7.2 years (range 1–21) of follow-up. One died after 6 years and two had recurrence. The other patients had no evidence of disease.

Treatment methods have been variable, yet all have had successful outcomes. Therapy includes observation, immobilization, NSAIDs [7, 15, 20, 28], chemotherapy [12, 34], radiotherapy, intralesional infiltration of steroids and surgery [30]. Recent case reports show encouraging results using the tumor necrosis factor- α (TNF- α) antagonist etanercept, the PPAR- γ antagonist pioglitazone, 2-Cda22 and the COX-2 antagonist rofecoxib to treat single-system disease [15]. Historically, patients with involvement localized to a single site usually receive local therapy, and those with multisystem disease require systemic chemotherapy. Treatment consensus is difficult to achieve because of the low incidence of LCH.

Immobilization

Spine immobilization is generally sufficient in reducing clinical symptoms, but there is no consensus even in this simplest treatment. Mammano et al. [22] suggested all the patients to remain in bed for a period of over 2 months, and the mean treatment time with corset was 42 months (range 20–60). Raab et al. suggested brace for 1–5 years. But Garg et al. [13] only applied spinal orthoses for comfort only for a few weeks following the biopsy. Yeom et al. [35] reported cases treated in three Korean hospitals, and they conservatively treated patients with/without immobilization. For us, immobilization is suggested for cases with pain or mild neurological symptoms; if the patient is asymptomatic, the immobilization could be abandoned.

Radiotherapy

Radiation therapy used to be popular for solitary bony lesions of LCH, but is abandoned by most authors for two possible complications, secondary malignancy and vertebral growth disturbance [4, 13, 20]. We still prefer radiotherapy for severe bony destruction and/or mild neurological deficit for two reasons. First, secondary malignancy following radiotherapy for LCH was only reported in 4 (4%) of 89 patients by Greenberger et al. [16], but there are no further similar complications in the literature. Second, vertebral growth disturbance by radiotherapy is possible theoretically, but has never been reported [11, 35]. Raab et al. [26] suggested a dosage between 8 and 12 Gy for children which was only indicated when immobilization failed to relieve the symptoms. This limited dosage could provide rapid and reliable pain relief without altering reconstitution potential and spinal growth.

Surgery

Classic indications for surgery included suspected malignancy, neurological symptoms, mechanical instability and deformity. There have been sporadic case reports of spinal lesions requiring surgical stabilization [30]. But Plasschaert and his colleagues [25] showed a low rate of recurrence in skeletally immature LCH patients and a higher rate in resection cases than less aggressive procedures. Yeom et al. [35] stated that patients who underwent surgery, especially curettage and anterior fusion, had the worst outcome.

Therefore, the treatment indications are still controversial. (1) Open biopsy for suspected malignancy now has very limited value with the technical development of percutaneous biopsy. When the result of needle biopsy is inconclusive, open biopsy might be indicated. In these 55 cases, only 8 had open biopsy. (2) There are no clear criteria for instability and deformity. Mammano et al. [22] had good clinical result only by immobilization. (3) The treatment of children with neurologic deficit is more controversial [10]. Some have advocated that immobilization and radiation are appropriate in children with mild neurologic deficit, but others believe that the neural elements should be decompressed and then fused, with the debatable addition of radiation or chemotherapy [35]. In the literature, neurologic symptoms were usually mild and progressed slowly, therefore emergency surgical decompression seems unnecessary. In Garg's [13] 11 cases, none had neurological deficit, although some had neurological symptoms (radiating pain or gait abnormalities) which resolved with conservative treatments. Neurologic function could also recover after surgery, but vertebral height did not recover from the physal damage during surgery [35]. In cases involving children, anterior fusion gave rise to progressive kyphosis, possibly requiring additional posterior fusion [30, 31].

With the better understanding of LCH, our present indications for spinal surgery are stabilization of an unstable spine segment that cannot be stabilized with an orthosis or severe neurologic symptoms due to compression of the spinal cord by the collapsed vertebra. For treatment of mild neurologic deficit, we prefer immobilization and low-dose radiotherapy.

Prognosis

The prognosis is generally fair, and depends largely on the visceral extension of lesions, although any effects of loading on the pathologic bone tissue (e.g. compression collapse and kyphoscoliosis) must be taken into account. The resolution from LCH occurred at a rate unaffected by the mode of treatment [2, 14]. There is no clear evidence

Fig. 4 Proposed protocol for the management of LCH with multifocal spinal lesions. Asterisk indicates typical presentation means for multifocal lesions with vertebra plana without posterior arch, epidural and paravertebral extension

that treatment affects the natural history of this entity. Robert pointed out that the spinal complications in LCH are due more to the aggressiveness of the therapy than the natural progression of the condition itself. Many investigators have reported that satisfactory, though not always complete, reconstitution of vertebral height usually occurs regardless of treatment [35]. Only two cases had recurrence in this review.

Proposed protocol

On the basis of the results of this study and a review of the literature, we propose the following protocol for the management of LCH with the multifocal spinal lesions (Fig. 4).

In 1987, Robert et al. [27] pointed out that the orthopedic surgeons has a threefold role in the treatment of LCH: to certify the diagnosis in localized forms and some diffused forms, to place the spine in a rest position and to follow the patient to detect possible progressive relapse and treat them.

In conclusion, only an evaluation of greater numbers of these critical patients in the frame of cooperative multicentric studies will contribute to define the optimal diagnosis and treatment strategy for this particular disease manifestation. Continuous spinal lesion could be treated as isolated lesion, asymptomatic spinal lesions could be simply observed with or without bracing and chemotherapy justified for multiple lesions. Surgical decompression should be reserved for the uncommon cases in which

neurologic compromise does not respond to radiotherapy or progresses too rapidly for radiotherapy.

References

1. Aizawa T, Sato T, Tanaka Y, Kokubun S (2005) Signal intensity changes on MRI during the healing process of spinal Langerhans cell granulomatosis: report of two cases. *J Spinal Disord Tech* 18:98–101
2. Azouz EM, Saigal G, Rodriguez MM, Podda A (2005) Langerhans' cell histiocytosis: pathology, imaging and treatment of skeletal involvement. *Pediatr Radiol* 35:103–115
3. Bavbek M, Atalay B, Altinörs N, Caner H (2004) Spontaneous resolution of lumbar vertebral eosinophilic granuloma. *Acta Neurochir (Wien)* 146:165–167
4. Bertram C, Madert J, Eggers C (2002) Eosinophilic granuloma of the cervical spine. *Spine* 27:1408–1413
5. Brown CW, Jarvis JG, Letts M, Carpenter B (2005) Treatment and outcome of vertebral Langerhans cell histiocytosis at the Children's Hospital of Eastern Ontario. *Can J Surg* 48:230–236
6. Conway JJ (1996) Commentary. *Pediatr Radiol* 26:742–743
7. Denaro L, Longo UG, Papalia R, Di Martino A, Maffulli N, Denaro V (2008) Eosinophilic granuloma of the pediatric cervical spine. *Spine* 33:E936–E941
8. Dogan AS, Conway JJ, Miller JH, Grier D, Bhattathiry MM, Mitchell CS (1996) Detection of bone lesions in Langerhans cell histiocytosis: complementary roles of scintigraphy and conventional radiography. *J Pediatr Hematol Oncol* 18:51–58
9. 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 (1997) Contemporary classification of histiocytic disorders. The WHO Committee on histiocytic/reticulum cell

- proliferations. Reclassification working group of the Histiocyte Society. *Med Pediatr Oncol* 29:157–166
10. Fernando Ugarriza L, Cabezudo JM, Porras LF, Lorenzana LM (2003) Solitary eosinophilic granuloma of the cervicothoracic junction causing neurological deficit. *Br J Neurosurg* 17:178–181
 11. Floman Y, Bar-On E, Mosheiff R, Mosheiff R, Mirovsky Y, Robin GC, Ramu N (1997) Eosinophilic granuloma of the spine. *J Pediatr Orthop B* 6:260–265
 12. Gadner H, Grois N, Arico M, Broadbent V, Ceci A, Jakobson A, Komp D, Michaelis J, Nicholson S, Pötschger U, Pritchard J, Ladisch S, Histiocyte Society (2001) A randomized trial of treatment for multisystem Langerhans' cell histiocytosis. *J Pediatr* 138:728–734
 13. Garg S, Mehta S, Dormans JP (2004) Langerhans cell histiocytosis of the spine in children. Long-term follow-up. *J Bone Joint Surg Am* 86A:1740–1750
 14. Ghanem I, Tolo VT, D'Ambra P, Malogalowkin MH (2003) Langerhans cell histiocytosis of bone in children and adolescents. *J Pediatr Orthop* 23:124–130
 15. Goldberg SA, O'Connor SC, Sprinz PG (2008) Prostaglandin inhibitors in the treatment of single-system Langerhans cell histiocytosis: pharmacologic rationale and report of two cases. *J Pediatr Hematol Oncol* 30:778–780
 16. Greenberger JS, Crocker AC, Vawter G, Jaffe N, Cassady JR (1981) Results of treatment of 127 patients with systemic histiocytosis. *Medicine (Baltimore)* 60:311–338
 17. Hoover KB, Rosenthal DI, Mankin H (2007) Langerhans cell histiocytosis. *Skelet Radiol* 36:95–104
 18. Howarth DM, Gilchrist GS, Mullan BP, Wiseman GA, Edmonson JH, Schomberg PJ (1999) Langerhans cell histiocytosis: diagnosis, natural history, management, and outcome. *Cancer* 85:2278–2290
 19. Islinger RB, Kuklo TR, Owens BD, Horan PJ, Choma TJ, Murphey MD, Temple HT (2000) Langerhans' cell histiocytosis in patients older than 21 years. *Clin Orthop Relat Res* 379:231–235
 20. Levine S, Dormans J, Meyer J, Corcoran TA (1996) Langerhans' cell histiocytosis of the spine in children. *Clin Orthop* 323:288–293
 21. Levy EI, Scarrow A, Hamilton RC, Wollman MR, Fitz C, Pollack IF (1999) Medical management of eosinophilic granuloma of the cervical spine. *Pediatr Neurosurg* 31:159–162
 22. Mammano S, Candiotti S, Balsano M (1997) Cast and brace treatment of eosinophilic granuloma of the spine: long-term follow-up. *J Pediatr Orthop* 17:821–827
 23. Nesbit ME, Kieffer S, D'Angio GJ (1969) Reconstitution of vertebral height in histiocytosis X: a long-term follow-up. *J Bone Joint Surg Am* 51:1360–1368
 24. Papagelopoulos PJ, Currier BL, Galanis EC et al (1999) Vertebra plana of the lumbar spine caused by an aneurysmal bone cyst: a case report. *Am J Orthop* 28:119–124
 25. Plasschaert F, Craig C, Bell R, Cole WG, Wunder JS, Alman BA (2002) Eosinophilic granuloma. A different behaviour in children than in adults. *J Bone Joint Surg Br* 84:870–872
 26. Raab P, Hohmann F, Kühl J, Krauspe R (1998) Vertebral remodeling in eosinophilic granuloma of the spine. A long-term follow-up. *Spine* 23:1351–1354
 27. Robert H, Dubousset J, Miladi L (1987) Histiocytosis X in the juvenile spine. *Spine* 12:167–172
 28. Sessa S, Sommelet D, Lascombes P, Prévot J (1994) Treatment of Langerhans-cell histiocytosis in children. *J Bone Joint Surg Am* 76:1513–1525
 29. Shisha T, Kiss S, Varga PP, Bucsi L, Pap K, Szoke G (2006) Osteochondritis (Calvé's disease) of a vertebral body—a rare form of vertebra plana. *Eur Spine J* 15:377–383
 30. Sohn MJ, Park HC, Park HS, Kim JJ, Kim EY (2001) Anterior cervical corpectomy and fusion using miniplate and screws in a 7-year-old child with eosinophilic granuloma of the cervical spine. *Spine* 26:1193–1196
 31. Tan G, Samson I, De Wever I, Goffin J, Demaerel P, Van Gool SW (2004) Langerhans cell histiocytosis of the cervical spine: a single institution experience in four patients. *J Pediatr Orthop B* 13:123–126
 32. Tanaka N, Fujimoto Y, Okuda T, Nakanishi K, Sumida T, Manabe H, Ochi M (2005) Langerhans cell histiocytosis of the atlas. A report of three cases. *J Bone Joint Surg Am* 87:2313–2317
 33. Vadivelu S, Mangano FT, Miller CR, Leonard JR (2007) Multifocal Langerhans cell histiocytosis of the pediatric spine: a case report and literature review. *Childs Nerv Syst* 23:127–131
 34. von Stebut E, Schadmand-Fischer S, Bräuninger W, Kreft A, Doberauer C, Steinbrink K (2008) Successful treatment of adult multisystemic Langerhans cell histiocytosis with psoralen-UV-A, prednisolone, mercaptopurine, and vinblastine. *Arch Dermatol* 144:649–653
 35. Yeom JS, Lee CK, Shin HY, Lee CS, Han CS, Chang H (1999) Langerhans' cell histiocytosis of the spine. Analysis of twenty-three cases. *Spine* 24:1740–1749