Langerhans cell histiocytosis: update for the pediatrician

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Purpose of review

Langerhans cell histiocytosis is the commonest of the histiocytic disorders. Owing to the relative rarity of the condition, it remains a disease in which the diagnosis is often delayed or missed and in which many questions remain unanswered, ranging from etiology and pathogenesis to therapy. The management is often frustrating for care-givers and parents/patients. The purpose of the review is therefore to raise awareness of the disease and to highlight the clinical findings that should make the pediatrician or primary care-giver suspect the diagnosis, as well as current thinking regarding management of the various and diverse manifestations of this disease.

Recent findings

We discuss new and interesting insights into the biology of Langerhans cell histiocytosis that raise the possibility of future targeted therapy. Important points in the diagnosis, investigation and management of the various forms of the disease are also discussed.

Summary

We present a review of childhood Langerhans cell histiocytosis, highlighting new insights into pathogenesis and management of the various forms of this complex disease.

Keywords

dendritic cell, Langerhans cell histiocytosis, pediatric, review

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Introduction

Langerhans cell histiocytosis (LCH), a disorder of antigen-presenting cells, is the commonest disorder of the mononuclear phagocytic system. Owing to the relative rarity of the condition, it remains a disease in which the diagnosis is often delayed or missed and in which many questions remain unanswered, ranging from etiology and pathogenesis to therapy.

The article is not intended as a comprehensive review of LCH, but is intended instead to discuss some recent advances in the biology of the disease as well as advances in therapy and to highlight important points for the pediatricians who care for these patients [1••,2,3•,4,5,6•].

LCH is characterized by clonal proliferation and excess accumulation of pathologic Langerhans cells. The disease varies widely in clinical presentation from localized involvement of a single bone to a widely disseminated life-threatening disease.

Diagnosis of Langerhans cell histiocytosis

The diagnosis is clinicopathologic, based on classical clinical findings and histologic/immunohistochemical criteria, to avoid misdiagnosis of reactive normal Langerhans cells found within nodes in response to a variety of diseases including neoplasms [7,8]. Previously absolute criteria for diagnosis depended on finding CD1a by immunohistochemistry or Birbeck granules by electron microscopy. Currently, the presence of Birbeck granules is assumed by immunohistochemical demonstration of langerin (CD207), a mannose-specific lectin whose intracellular component is found in association with Birbeck granules with 100% concordance [1••]. Positivity of one or both of these markers now defines the Langerhans cell phenotype [2,9].

Histopathology

The histopathology of LCH is that of a granulomatous lesion containing pathologic Langerhans cells as well as normal inflammatory cells such as T cells, eosinophils and macrophages, together with multinucleated giant cells. The latter were recently shown to be osteoclast-like and able to produce cytokines that can cause osteolysis [10].

Pathogenesis

In LCH, the pathologic LCH cells appear to be in an arrested state of activation and/or differentiation [11]. LCH cells are prevented from leaving their peripheral tissue sites, where they accumulate and express

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inflammatory chemokines, resulting in their own recruitment and retention, as well as that of other inflammatory cells including T lymphocytes [2]. It has long been known that erratic and uncontrolled production of various cytokines creates a 'cytokine storm' [12]. The pattern of cytokine expression favors recruitment of Langerhans cell progenitors, as well as their maturation and rescue from apoptosis, thereby explaining the pathologic accumulation of LCH cells [12–14]. The cytokines produced directly contribute to the pathologic sequelae, including fibrosis, bone resorption and necrosis.

Of recent interest is the role of the multinucleated giant cell (MNGC). These cells are osteoclast-like and able to cause osteonecrosis [10]. Furthermore, it has been demonstrated that normal dendritic cells can fuse to form MNGCs in the presence of macrophage colony-stimulating factor and receptor activator of NF-κB ligand (RANKL) [15], both of which are highly expressed by LCH cells [10]. Paradoxically, however, the transdifferentiation of dendritic cells into MNGCs is inhibited by interferon-γ, a cytokine found in abundance in LCH lesions [16], produced by LCH cells, T cells and macrophages [12]. Investigators, therefore, are seeking a different mechanism for development of the MNGCs that appear to play an important role in LCH lesions. Recognition of such a mechanism will allow the development of more specific targeted therapies for all forms of LCH.

Etiology of Langerhans cell histiocytosis

The discovery that all forms of LCH except adult pulmonary LCH are monoclonal [17,18] suggests that this may be a neoplastic process with varying biologic behavior. Monoclonality is not proof of malignancy, however, and a case can be made both for and against this being primarily a malignant disease [2]. Recent findings of loss of heterozygosity on chromosomes 1, 4, 6, 7, 9,16, 17 and 22, as well as chromosomal instability and elevated expression of cell-cycle-related proteins or oncogene products, such as p53, H-*ras* and c-*myc*, suggesting disrupted cell-cycle regulation, are more persuasive evidence of neoplasia [2,19–21].

Recent studies of telomerase expression by CD1a cells in LCH lesions [22], as well as the telomere length shortening in Langerhans cells in all stages of disease [23], lend support to this being a neoplastic disorder, although the possibility of an initiating infectious, malignant or immune event is still possible [23]. An alternative hypothesis is that this is a reactive disease, resulting from environmental or other triggers, which lead to the aberrant reaction between Langerhans cells and T lymphocytes [24].

In adults, cigarette smoking is a clear risk factor for pulmonary LCH. The exact relationship of this sometimes polyclonal lung disease to the monoclonal forms of the disease remains to be elucidated, particularly in view of a Swedish study which raised the possibility of an increased risk for the development of lung LCH in adult survivors of pediatric LCH who smoke [25].

Clinical presentation of Langerhans cell histiocytosis

LCH can present at any age from the neonate until old age. It has become increasingly clear that patients present mainly with three different forms of disease. At one end of the spectrum are patients with single-system disease with a 100% survival with minimal or no therapy. At the other end are patients, usually very young children, with disseminated life-threatening LCH that can involve any organ, although kidney and gonad are usually spared. Between the two extremes are patients whose disease runs a chronic fluctuating course that eventually 'burns out', but often leaves serious residual disabilities [2]. See Table 1 for a brief summary of clinical features of pediatric LCH.

Bone involvement in Langerhans cell histiocytosis

Bone is the commonest single organ in childhood LCH and the majority present with a single bone lesion with an excellent outcome. The commonest presentation of LCH in childhood is with a single mass lesion on the skull. All bones may be involved, however, except for the hands and feet. The usual presentation is with swelling and/or pain that initially may be present only at night [26]. LCH is the commonest cause of vertebra plana in children [27] and an associated soft tissue mass may result in significant neurologic impairment [28,29]. In most single bone lesions, curettage of the center of the lesion gives diagnostic tissue and usually starts the healing process. Surgical resection is unnecessary and may lead to long-term deformity. Observation is limited to lesions in 'nonrisk' bones, in patients with a pathologic diagnosis [30].

Controversy exists regarding 'special site' bones in the anterior part of the skull, face and base of skull. Most will heal with curettage alone, but those that have a significant soft tissue component extending internally, particularly if it involves the dura, should be considered as risk bones for progression to diabetes insipidus and neurologic disease, and should be candidates for low-risk chemotherapy (Grois, personal communication). Low-dose radiation therapy remains an effective modality, but it is usually restricted to involvement of critical organs such as the spinal cord or optic nerve.

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Table 1 Summary of clinical features of LCH in children

Subtype	Median age (years)	Therapy	Survival (%)	Reactivation rate (%)	Diabetes insipidus rate (%)
Single system					
Bone-only					
Unifocal bone	5	curettage intralesional steroid low-dose radiation therapy[a]	100	3–12	3
special site with intracranial extension		biopsy plus chemotherapy (vinblastine/prednisone)			
vertebra plana without mass		observation[b]			
Multifocal bone	2–5	biopsy plus chemotherapy (vinblastine/prednisone) nonsteroidal anti-inflammatory drugs bisphosphonates	100	25	15
Skin-only	0–adult	biopsy observation topical steroid topical tacrolimus excision (no mutilating surgery) chemotherapy other	100[c]		occasional report
Multisystem					
Risk[d] (two or more organs including hematopoietic ± liver ± spleen[e])	<2	biopsy plus chemotherapy (vinblastine/prednisone/6-mercaptopurine ± methotrexate) × 12 months[f]	80	50	30–50
Low risk (two or more organs; no risk organs)	4	biopsy plus chemotherapy (vinblastine/prednisone/6-mercaptopurine) × 6–12 months[f]	99	30–50	30–50

[a] Limited to involvement of critical organs, i.e. spinal cord, optic nerve.
[b] Vertebra plana without a soft tissue mass can be carefully observed without a biopsy.
[c] Neonates and young infants with skin-only LCH may progress to 'risk' multisystem disease with a much lower survival.
[d] Risk for mortality.
[e] Although still included in current protocols, lung as the only risk organ will not = 'risk' LCH in future trials.
[f] Duration of therapy is based on the current open randomized trial (LCH-III) and may change depending on the outcome. Other study group protocols include other drugs, including vincristine, cytosine arabinoside and doxorubicin.

For single or multiple lesions, indomethacin, a potent prostaglandin E_2 inhibitor, and other nonsteroidal anti-inflammatory drugs (NSAIDs), have proven efficacious [31,32]. The use of bisphosphonates [33–35] is supported by the report of da Costa *et al.*, who demonstrated that the bony destruction is likely mediated by osteoclast-like giant cells that produce matrix-degrading enzymes, resulting in destructive lesions and bone pain [10]. The role of NSAIDs and bisphosphonates in preventing reactivations and late complications is unclear, as is the long-term effect of bisphosphonates in young children.

Evaluation of response in bone is difficult. [^{18}F]Fluorodeoxyglucose (FDG)-PET, a sensitive technique for identifying metabolically active LCH, has been shown to detect more lesions than conventional methods at diagnosis and reactivation, and FDG avidity correlates with response [36]. Availability, expense, irradiation dose and need for sedation in young children may limit its utility. Reactivations occur at a rate of 3–12% for unifocal bone, 11–25% for multifocal bone and 50–70% for bone as part of multisystem LCH [5]. The greater the reactivation rate, the higher the incidence of diabetes insipidus and other late complications [3•]. A recent study comprising 300 patients from Argentina showed that permanent consequences occurred in 71% of patients with reactivations [37].

Important points for the pediatrician regarding bone LCH include the following:

- LCH should be considered in all young patients who present with a skull mass, jaw pain, swelling and/or loose teeth, chronic ear drainage, with dermatitis of the auricular canal, mastoiditis and cholesteatoma [38,39] or proptosis, swelling and redness of the eyelid.
- The classical radiologic finding is a punched-out lytic lesion in bone, but some LCH lesions can resemble an aggressive bone sarcoma with destruction of bone and periosteal elevation [40]. This is seen particularly in facial or base of skull lesions, but may be seen in long bones.
- Biopsy to confirm the diagnosis is necessary for all lesions except those presenting with vertebra plana without a soft tissue mass, when the risk of biopsy outweighs the potential benefit. These patients need careful follow-up to exclude malignancy.
- Multifocal bone and bone associated with multisystem LCH are treated for two reasons, to treat pain, but

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more importantly to try to prevent permanent consequences.

Skin Langerhans cell histiocytosis

Skin involvement occurs in 50% of patients with isolated 'skin-only' disease in about 10% [41•]. The commonest presentation is with a 'seborrhea-like' eruption, which may or may not be purpuric, often initially misdiagnosed as 'cradle-cap'. Other skin manifestations include papules, vesicles, crusted plaques, nodules and purpuric nodules [42]. Patients with skin-only LCH may have spontaneous regression, regression and reactivation in skin or progression, particularly in the infant, to disseminated, sometimes fatal disease. Hashimoto–Pritzker disease (congenital self-healing reticulohistiocytosis) is a skin-only LCH associated with spontaneous involution. There are no reliable pathologic criteria that distinguish congenital self-healing reticulohistiocytosis from skin LCH, and a recent study failed to show a significant difference in histology or expression of markers such a E-cadherin, Ki-67 and phosphorylated histone 3 [43].

Important points for the pediatrician are:

(1) LCH should be considered whenever seborrheic dermatitis or diaper dermatitis fails to respond to therapy, or keeps recurring.
(2) All young babies with skin-only LCH should be carefully followed [44,45,41•] as approximately 50% will progress to multisystem disease, which may be fatal [41•].
(3) In general skin-only LCH has a good prognosis and should not be overtreated. Surgical excision should be undertaken for small isolated lesions only and no mutilating surgery is ever necessary.

Multisystem Langerhans cell histiocytosis

For therapeutic purposes multisystem LCH is divided into two categories based on the risk of mortality from disease. Risk LCH includes all patients with disease in two or more organs including a risk organ, defined until recently as involvement of liver, spleen, lung and hematopoietic system. The latter is defined by the presence of anemia, neutropenia and/or thrombocytopenia, and is not excluded by the absence of morphologic infiltration of bone marrow [38,46]. Hematopoietic disease may be associated with secondary hemophagocytosis – a common finding in young patients who died from disease in a French study (Donadieu, personal communication). Recently several studies have concluded that, in pediatric patients, lung involvement as the only 'risk' organ does not give an increased risk of death and lung will be removed as a 'risk' organ in future Histiocyte Society studies.

Central nervous system/endocrine involvement

Hypothalamic–pituitary axis (HPA) disease is considered to be a major risk factor for central nervous system (CNS) LCH. Diabetes insipidus occurs in about 24% of patients overall [47] and is commonest in patients with multisystem LCH [37,47]. Diabetes insipidus may present at diagnosis (6% of 1741 patients in a recent review [3•]) or it may occur later, usually in patients with the chronically reactivating form of the disease [3•,37]. Anterior pituitary deficits may follow diabetes insipidus [48], and include growth hormone deficiency, precocious or delayed puberty, thyroid deficiency, amenorrhea, hyperprolactinemia, morbid obesity [49], sleeping disorders and disorders of thermoregulation [50]. The risk of other endocrinopathies in diabetes insipidus patients may be as high as 57% at 10 years after diabetes insipidus onset [3•]. Treatment of growth hormone deficiency with growth hormone has proven to be safe and effective, and did not induce reactivations or second malignancies [51]. Most cases of diabetes insipidus are irreversible at presentation. Nonetheless, the current recommendation is to treat recent-onset diabetes insipidus to try to prevent the other late effects. Optimal therapy, however, is unclear. Owing to the potential for late effects, radiation therapy should be restricted to nonresponsive growing masses [52]. The pituitary is outside the blood–brain barrier (BBB) and standard LCH chemotherapy as well as drugs, such as 2-chlorodeoxyadenosine (2-CdA), which cross the BBB will likely treat active HPA-LCH. Dhall *et al.* [53] found that eight of 12 patients treated with 2-CdA for CNS mass lesions had a complete response, while four had a sustained partial response. Eleven of 12 remained progression-free. There was, however, no reversal of neurocognitive dysfunction and/or diabetes insipidus that was already present at the time of therapy.

Nonendocrine central nervous system involvement

Active CNS LCH, first seen as extra-parenchymal lesions in areas where the BBB is deficient (leptomeninges, choroid plexus, pineal gland) may progress to chronic neurodegeneration due to demyelination and gliosis from cytokine/chemokine-mediated neural damage [54] or an autoimmune reaction to the preceding LCH [55]. This devastating end-stage disease is observed in 3–5% of patients with LCH, but may occur in 10% or more of patients with diabetes insipidus. Clinical findings include cerebellar dysfunction, psychomotor retardation and neuropsychologic problems with severe disability and even death [55,56]. It is unclear how many asymptomatic patients with neurodegeneration seen on MRI scans will progress to debilitating symptomatic neurodegeneration. Brain-stem evoked potentials have proved useful in

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detecting subtle abnormalities [6•]. Brain FDG-PET scans may be helpful in defining active as well as burnt-out lesions [57]. There is no known effective therapy for patients with late progressive CNS disease. Prevention of reactivations and of diabetes insipidus is likely to be very important in prevention of late effects.

Permanent consequences

Results of the late effects study of the Histiocyte Society suggest that, with a minimum of 3 years of follow-up, at least 71% of multisystem and 24% of single-system patients have at least one permanent consequence, the most commonly reported being diabetes insipidus [4,37]. Other than the CNS permanent consequence discussed above, orthopedic problems, facial asymmetry, residual proptosis, loss of teeth and hearing loss are seen. Second malignancies, particularly acute T lymphoblastic leukemia, occur in LCH patients with a much higher than expected frequency [4]. Others include solid tumors, lymphoma and myeloid and lymphoid leukemias.

Most of the serious permanent consequences occur in patients with multisystem disease with lesions involving the facial bones and base of skull, particularly those whose disease has a chronically relapsing and remitting course [3•], and particular attention needs to be paid to the therapy of these patients. Extensive surgical resections should be avoided, and the use of carcinogenic drugs and radiation therapy should be limited to life-threatening situations.

Treatment of multisystem Langerhans cell histiocytosis

Treatment of multisystem LCH is given to improve survival and to prevent late sequelae. Patients with extensive disease, but without involvement of 'risk' organs, have an excellent survival with minimal therapy. For patients with 'risk' multisystem LCH, results of the large randomized cooperative group trials suggest that early therapy with relatively nontoxic chemotherapy improves survival and may reduce the incidence of late complications [46,58–60]. All these studies show that a lack of response to chemotherapy at 6 weeks is the single most important predictor of poor survival [47,59,61]. Poor responders have a very poor outcome, but recent data from the Japanese LCH study group [60], as well as a French pilot study using 2-CdA and high-dose cytosine arabinoside (ara-C) [62], suggest that early switch of poor responders to intensive salvage regimens improves survival. The majority of patients who fail these intensive salvage regimens die and hematopoietic stem cell transplantation (SCT) should be considered early for this group. A review of the literature found 15/27 (56%) patients alive in continuous complete remission (median 25 months) following allogeneic SCT [62]. The major cause of failure was transplant-related mortality [63]. LCH may be an ideal disease for reduced intensity conditioning, as suggested by the survival of nine of 11 patients in a recent study [64]. This concept is the subject of an open Histiocyte Society study, designed for patients who fail the 2-CdA/ara-C salvage study.

For patients who respond to initial therapy, survival is very good. Reactivation, if it occurs, usually occurs in nonrisk organs such as skin or bone and is rarely fatal; however, permanent consequences occur in as many as 70% of patients [4].

One of the major challenges facing investigators is to design therapy that prevents reactivations and hopefully the significant permanent consequences. Review of 391 multisystem patients registered on LCH-II showed that for multifocal bone patients local therapy resulted in a 52% reactivation rate, compared with 45% with single-drug and 20% with two-drug therapy [3•]. In addition, retrospective evidence of a significantly decreased incidence of diabetes insipidus in the German DAL studies, which gave therapy for 12 months [58] rather than the 6 months utilized in most other studies, suggests that prolonged low-toxicity therapy may be optimal for chronically reactivating disease. The open LCH-III protocol is, in part, designed to determine whether prolongation of therapy can reduce reactivations in low and high-risk multisystem LCH patients.

Late chronic Langerhans cell histiocytosis

Late fibrosis, possibly due to the effect of excess inflammatory cytokines such as transforming growth factor-β [65], may occur in liver or lung. Late chronic liver disease presents as sclerosing cholangitis and biliary cirrhosis progressing to liver failure [66,67] while in the lungs progression to pulmonary fibrosis may lead to respiratory failure [68]. Clinically and radiographically, it is difficult to differentiate active LCH from end-stage fibrosis [69,70]. Organ transplantation is the only proven effective therapy for end-stage lung and liver disease, and the results appear to be durable for most patients, although recurrence of LCH in the transplanted organ has been described [68,71].

Conclusion

LCH remains a dilemma for treating physicians. Despite the relative rarity of the disease, pediatricians need to maintain awareness of the condition in order to reduce the delay in diagnosis and therapy, and to minimize the frustration felt by parents/patients. In this review, we have attempted to highlight a few of the major advances

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in dendritic cell biology that may lead to advances in targeted therapies.

From a clinical viewpoint, some important points to emerge from recent studies suggest the following. Single-system disease has a good outcome and should not be overtreated. High-risk multisystem LCH needs therapy to improve survival. Early response to therapy is the most important predictor of survival and early change to salvage therapy of poor responders appears to reduce mortality. Patients with low-risk multisystem and single-system multifocal bone disease require therapy to prevent reactivations and permanent consequences. Multiagent chemotherapy and prolonged therapy appear to be of value in this regard, but the drugs needed and the length of therapy required need to be determined in prospective trials.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 109).

1 •• Bechan GI, Egeler RM, Arceci RJ. Biology of Langerhans cells and Langerhans cell histiocytosis. Int Rev Cytol 2006; 254:1–43.
This article discusses the biology of normal Langerhans cells and LCH cells in detail.

2 Beverley PC, Egeler RM, Arceci RJ, Pritchard J. The Nikolas Symposia and histiocytosis. Nat Rev Cancer 2005; 5:488–494.

3 • Grois N, Pötschger U, Prosch H, *et al.* Risk factors for diabetes insipidus in Langerhans cell histiocytosis. Pediatr Blood Cancer 2006; 46:228–233.
This gives a detailed assessment of risk factors for this important complication based on a large number of patients.

4 Haupt R, Nanduri V, Egeler RM. Late effects of Langerhans cell histiocytosis and its association with malignancy. In: Weitzman S, Egeler RM, editors. Histiocytic disorders of children and adults. Cambridge: Cambridge University Press; 2005. pp. 272–292.

5 Lau L, Stuurman K, Weitzman S. Skeletal Langerhans cell histiocytosis in children: permanent consequences and health-related quality of life in long term survivors. Pediatr Blood Cancer 2007 [Epub ahead of print].

6 • Mittheisz E, Seidl R, Prayer D, *et al.* Central nervous system-related permanent consequences in patients with Langerhans cell histiocytosis. Pediatr Blood Cancer 2007; 48:50–60.
This article discusses the most important of the potential permanent consequences of LCH in children.

7 Jaffe R. The diagnostic histopathology of Langerhans cell histiocytosis. In: Weitzman S, Egeler RM, editors. Histiocytic disorders of children and adults. Cambridge: Cambridge University Press; 2005. pp. 14–39.

8 Christie LJ, Evans AT, Bray SE, *et al.* Lesions resembling Langerhans cell histiocytosis in association with other lymphoproliferative disorders: a reactive or neoplastic phenomenon? Hum Pathol 2006; 37:32–39.

9 Romani N, Holzmann S, Tripp CH, *et al.* Langerhans cells – dendritic cells of the epidermis. APMIS 2003; 111:725–740.

10 Da Costa CE, Annels NE, Faaij CM, *et al.* Presence of osteoclast-like multinucleated giant cells in the bone and nonostotic lesions of Langerhans cell histiocytosis. J Exp Med 2005; 201:687–693.

11 Annels NE, Da Costa CET, Prins FA, *et al.* Aberrant chemokine receptor expression and chemokine production by Langerhans cells underlies the pathogenesis of Langerhans cell histiocytosis. J Exp Med 2003; 197:1385–1390.

12 Egeler RM, Favara BE, Van Meurs M, *et al.* Differential *in situ* cytokine profiles of Langerhans-like cells and T cells in Langerhans cell histiocytosis: abundant expression of cytokines relevant to disease and treatment. Blood 1999; 94:4195–4201.

13 Geissmann F, Lepelletier Y, Fraitag S, *et al.* Differentiation of Langerhans cells in Langerhans cell histiocytosis. Blood 2001; 97:1241–1248.

14 Tazi A, Moreau J, Bergeron A, *et al.* Evidence that Langerhans cells in adult pulmonary Langerhans cell histiocytosis are mature dendritic cells: importance of the cytokine microenvironment. J Immunol 1999; 163:3511–3515.

15 Speziani C, Rivollier A, Gallois A, *et al.* Murine dendritic cell transdifferentiation into osteoclasts is differentially regulated by innate and adaptive cytokines. Eur J Immunol 2007; 37:747–757.

16 Delprat C. Mechanisms of dendritic cell-derived giant cell formation and LCH. Proceedings of the 23rd Annual Meeting of Histiocyte Society. Cambridge; 2007. p. 14.

17 Willman CL, Busque L, Griffiths BB, *et al.* Langerhans cell histiocytosis – a clonal proliferation of Langerhans cells. N Engl J Med 1994; 331:154–160.

18 Yu RC, Chu C, Buluwela L, Chu AC. Clonal proliferation of Langerhans cells in Langerhans cell histiocytosis. Lancet 1994; 343:767–768.

19 Murakami I, Gogusev J, Fournet JC, *et al.* Detection of molecular cytogenetic aberrations in Langerhans cell histiocytosis of bone. Hum Pathol 2002; 33:555–560.

20 Betts DR, Leibundgut KE, Feldges A, *et al.* Cytogenetic abnormalities in Langerhans cell histiocytosis. Br J Cancer 1998; 77:552–555.

21 Schouten B, Egeler RM, Leenen PJ, *et al.* Expression of cell cycle-related gene products in Langerhans cell histiocytosis. J Pediatr Hematol Oncol 2002; 24:727–732.

22 Da Costa CE, Egeler RM, Hoogeboom M, *et al.* Differences in telomerase expression by the $CD1a^{+}$ cells in Langerhans cell histiocytosis reflect the diverse clinical presentation of the disease. J Pathol 2007; 212:188–197.

23 Bechan GI, Meeker AK, De Marzo AM, *et al.* Telomere length shortening in Langerhans cell histiocytosis. Proceedings of the 23rd Annual Meeting of Histiocyte Society. Cambridge; 2007. p. 34.

24 Glotzbecker MP, Carpentieri DF, Dormans JP. Langerhans cell histiocytosis: clinical presentation, pathogenesis, and treatment from the LCH etiology research group at the Children's Hospital of Philadelphia. Univ Pa Orthop J 2002; 15:67–73.

25 Bernstrand C, Cederlund K, Åhstrom L, Henter J-I. Smoking preceded pulmonary involvement in adults with Langerhans cell histiocytosis diagnosed in childhood. Acta Paediatr 2000; 89:1389–1392.

26 Fernández-Latorre F, Menor-Serrano F, Alonso-Charterina S, Arenas-Jiménez J. Langerhans' cell histiocytosis of the temporal bone in pediatric patients. AJR Am J Roentgenol 2000; 174:217–221.

27 Kamimura M, Kinoshita T, Itoh H, *et al.* Eosinophilic granuloma of the spine: early spontaneous disappearance of tumor detected on magnetic resonance imaging. J Neurosurg 2000; 93 (2 Suppl):312–316.

28 Guzey FK, Bas NS, Emel E, *et al.* Polyostotic monosystemic calvarial and spinal Langerhans cell histiocytosis treated by surgery and chemotherapy. Pediatr Neurosurg 2003; 38:206–211.

29 Turgut M, Gurcay O. Multifocal histiocytosis X of bone in two adjacent vertebrae causing paraplegia. Aust N Z J Surg 1992; 62:241–244.

30 Egeler RM, Thompson RC, Voûte PA, Nesbit ME. Intralesional infiltration of corticosteroids in localized Langerhans cell histiocytosis. J Pediatr Orthop 1992; 12:811–814.

31 Munn SE, Olliver L, Broadbent V, Pritchard J. Use of indomethacin in Langerhans cell histiocytosis. Med Pediatr Oncol 1999; 32:247–249.

32 Arceci RJ, Brenner MK, Pritchard J. Controversies and new approaches to treatment of LCH. Hematol Oncol Clin North Am 1998; 12:339–357.

33 Brown RE. Bisphosphonates as antialveolar macrophage therapy in pulmonary Langerhans cell histiocytosis. Med Pediatr Oncol 2001; 36:641–643.

34 Farran RP, Zaretski E, Egeler RM. Treatment of Langerhans cell histiocytosis with Pamidronate. J Pediatr Hematol Oncol 2001; 23:54–56.

35 Kamizono J, Okada Y, Shirahata A, Tanaka Y. Bisphosphonate induces remission of refractory osteolysis in Langerhans cell histiocytosis. J Bone Joint Surg 2002; 17:1926–1928.

36 Kaste SC, Rodriguez-Galindo C, McCarville ME, Shulkin BL. PET-CT in pediatric Langerhans cell histiocytosis. Pediatr Radiol 2007; 37:615–622.

37 Pollono D, Rey G, Latella A, *et al.* Reactivation and risk of sequelae in Langerhans cell histiocytosis. Pediatr Blood Cancer 2007; 48:696–699.

38 Aricò M, Egeler RM. Clinical aspects of Langerhans cell histiocytosis. Hematol Oncol Clin North Am 1998; 12:247–258.

39 Koch B. Langerhans cell histiocytosis of temporal bone: role of magnetic resonance imaging. Top Magn Reson Imaging 2000; 11:66–74.

40 Hayes CW, Conway WF, Sundaram M. Misleading aggressive MR imaging appearance of some benign musculoskeletal lesions. Radiographics 1992; 12:1119–1134.

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

41 Lau L, Krafchik B, Trebo M, Weitzman S. Cutaneous Langerhans cell histio-
• cytosis in children under one year. Pediatr Blood Cancer 2006; 46:66–71. This article contains an important teaching point about skin-only LCH in the newborn and young infant.

42 Munn S, Chu AC. Langerhans cell histiocytosis of the skin. Hematol Oncol Clin North Am 1998; 12:269–286.

43 Kapur P, Erickson C, Rakheja D, *et al.* Congenital self-healing reticulohistiocytosis (Hashimoto–Pritzker disease): ten-year experience at Dallas Children's Medical Center. J Am Acad Dermatol 2007; 56:290–294.

44 Longaker MA, Frieden IJ, Le Boit PT, Sherertz EF. Congenital 'self-healing' Langerhans cell histiocytosis: the need for long term follow-up. J Am Acad Dermatol 1994; 31:910–916.

45 Esterly NB, Maurer HS, Gonzalez-Crussi F. Histiocytosis-X: a seven-year experience at a children's hospital. J Am Acad Dermatol 1985; 13:481–496.

46 Ladisch S, Gadner H, Aricó M, *et al.* A randomized trial of etoposide vs vinblastine in disseminated Langerhans cell histiocytosis. Med Pediatr Oncol 1994; 23:107–110.

47 The French LCH Study Group. A multicentre retrospective survey of LCH: 348 cases observed between 1983 and 1993. Arch Dis Child 1996; 75:17–24.

48 Maghnie M, Cosi G, Genovese E, *et al.* Central diabetes insipidus in children and young adults. N Engl J Med 2000; 343:998–1007.

49 Municchi G, Marconcini S, D'Ambrosio A, *et al.* Central precocious puberty in multisystem Langerhans cell histiocytosis: a case report. Pediatr Hematol Oncol 2002; 19:273–278.

50 Kaltsas GA, Powles TB, Evanson J, *et al.* Hypothalamo-pituitary abnormalities in adult patients with Langerhans cell histiocytosis: clinical, endocrinological and radiological features and response to treatment. J Clin Endocr Metab 2000; 85:1370–1376.

51 Maghnie M, Bossi G, Klersy C, *et al.* Dynamic endocrine testing and magnetic resonance imaging in the long term follow-up of childhood Langerhans cell histiocytosis. J Clin Endocr Metab 1998; 83:3089–3094.

52 Rosenzweig KE, Arceci R, Tarbell NJ. Diabetes insipidus secondary to Langerhans' cell histiocytosis: is radiation therapy indicated? Med Pediatr Oncol 1997; 29:36–40.

53 Dhall G, Finlay JL, Dunkel IJ, *et al.* Analysis of outcome for patients with mass lesions of the central nervous system due to Langerhans cell histiocytosis treated with 2-chlorodeoxyadenosine. Pediatr Blood Cancer; 2007 [Epub ahead of print].

54 Pritchard J. Acute ataxia complicating Langerhans cell histiocytosis. Arch Dis Child 2003; 88:178–179.

55 Grois N, Prosch H, Lassmann H, Prayer D. Central nervous system disease in Langerhans cell histiocytosis. In: Weitzman S, Egeler RM, editors. Histiocytic disorders of children and adults. Cambridge: Cambridge University Press; 2005. pp. 208–228.

56 Imashuku S, Okazaki NA, Nakayama M, *et al.* Treatment of neurodegenerative CNS disease in Langerhans cell histiocytosis with a combination of intravenous gammaglobulin and chemotherapy. Pediatr Blood Cancer; 2007 [E-pub ahead of print].

57 Calming U, Bernstrand C, Mosskin M, *et al.* Brain 18-FDG PET scan in central nervous system Langerhans cell histiocytosis. J Pediatr 2002; 141:435–440.

58 Grois N, Flucher-Wolfram B, Heitger A, *et al.* Diabetes insipidus in Langerhans cell histiocytosis: results from the DAL-HX 83 study. Med Pediatr Oncol 1995; 24:248–256.

59 Gadner H, Grois N, Arico M, *et al.* A randomized trial of treatment for multisystem Langerhans' cell histiocytosis. J Pediatr 2001; 138:728–734.

60 Morimoto A, Ikushima S, Kinugawa N, *et al.* Improved outcome in the treatment of pediatric multifocal Langerhans cell histiocytosis. Results from the Japan Langerhans Cell Histiocytosis Study Group-96 Protocol. Cancer 2006; 107:613–619.

61 Minkov M, Grois N, Heitger A, *et al.* Response to initial treatment of multisystem Langerhans cell histiocytosis: an important prognostic indicator. Med Pediatr Oncol 2002; 39:581–585.

62 Bernard F, Thomas C, Bertrand Y, *et al.* Multicentre pilot study of 2-chlorodeoxyadenosine and cytosine-arabinoside combined chemotherapy in refractory Langerhans cell histiocytosis with haematological dysfunction. Eur J Cancer 2005; 41:2682–2689.

63 Weitzman S, McClain K, Arceci R. Treatment of relapsed and/or refractory Langerhans cell histiocytosis. In: Weitzman S, Egeler RM, editors. Histiocytic disorders of children and adults. Cambridge: Cambridge University Press; 2005. pp. 254–271.

64 Steiner M, Matthes-Martin S, Attarbaschi A, *et al.* Improved outcome of treatment-resistant high-risk Langerhans cell histiocytosis after allogeneic stem cell transplantation with reduced-intensity conditioning. Bone Marrow Transplant 2005; 36:215–225.

65 Kelly M, Kolb M, Bonniaud P, Gauldie J. Re-evaluation of fibrogenic cytokines in lung fibrosis. Curr Pharm Des 2003; 9:39–49.

66 Marti L, Thomas C, Emilé JF, *et al.* Liver involvement in LCH. The French experience. Proceedings of the XIX Meeting of the Histiocyte Society. Philadelphia; 2003. p. 20.

67 Braier J, Ciocca M, Latella A, *et al.* Cholestasis, sclerosing cholangitis, and liver transplantation in Langerhans cell histiocytosis. Med Pediatr Oncol 2002; 38:178–182.

68 Tazi A, Hiltermann TJN, Vassallo R. Adult lung histiocytosis. In: Weitzman S, Egeler RM, editors. Histiocytic disorders of children and adults. Cambridge: Cambridge University Press; 2005. pp. 187–207.

69 Soler P, Bergeron A, Kambouchner M, *et al.* Is high resolution computed tomography a reliable tool to predict the histopathological activity of pulmonary Langerhans cell histiocytosis? Am J Respir Crit Care Med 2000; 162: 264–270.

70 Sundar KM, Gosselin MV, Chung HL, Cahill BC. Pulmonary Langerhans cell histiocytosis. Emerging concepts in pathobiology, radiology, and clinical evolution of disease. Chest 2003; 123:1673–1683.

71 Hadzic N, Pritchard J, Webb D, *et al.* Recurrence of Langerhans cell histiocytosis in the graft after pediatric liver transplantation. Transplantation 2000; 15:815–819.

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