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Review

Langerhans cell histiocytosis in adults: more questions than answers?

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Abstract

Langerhans cell histiocytosis (LCH) may affect patients of any age but in adults the features of this disease are still poorly defined. Most reports are based on single-specialty experience and there are only a few describing relatively large series of patients. Although child and adult patients share several features of the disease, and may either have localised or disseminated disease, the proportion of cases with lung involvement is much higher in adults and is partly explained by cigarette smoking. Persisting uncertainty about the pathogenesis of LCH has certainly limited current treatment alternatives. In particular, no clinical trial has been conducted in adults so far and most information derives from description of one or a few cases, often reported retrospectively. On the basis of the background provided by the data collected in its International Registry, the Histiocyte Society is about to start the first prospective, cooperative adult LCH study, aimed at: (a) establishing a common platform for clinical evaluation; (b) testing in adult patients the efficacy of the best standard chemotherapy regimen for children – a combination of prednisone and vinblastine – developed by the Society's trials; (c) describing the natural history of the disease, the impact of cigarette smoking withdrawal and the efficacy of steroid monotherapy in pulmonary LCH. Research studies, ancillary to this trial, offer unique opportunities of addressing some of the open questions in LCH including: the genetic component of the disease as supported by evidence of familial clustering and chromosomal instability, the issue of 'LCH cells' clonality, the relation between pulmonary disease, cigarette smoking, and immune system polymorphisms that might increase individual susceptibility to LCH. A concerted joint effort between paediatricians and adult specialists could be the key to the development of insights into LCH in all age groups affected by this distressing and often debilitating condition.

Keywords: Histiocytosis; Langerhans cell; Lung; Steroids; Chemotherapy

Langerhans cell histiocytosis (LCH) is a rare disease, regarded as being caused by the accumulation and proliferation of abnormal, bone marrow-derived Langerhans cells. These dendritic cells, together with lymphocytes, eosinophils and non-dendritic histiocytes, form infiltrates typical of the disease, which may be found in various organs and to different extents [1]. This tissue heterogeneity results in a wide range of clinical presentations, including those formerly defined as eosinophilic granuloma, Hand-Schüller-Christian syndrome and Letterer-Siwe disease [2,3]. The course of LCH is often unpredictable, varying from spontaneous regression and resolution to rapid progression and death or repeated recurrence and recrudescence with a considerable risk of permanent sequelae. Patients with disease that is localised to one organ system – 'single system' disease – usually in the bone, skin or lymph nodes, have a good prognosis and seem to need minimal or even no treatment. In contrast, multiple organ involvement – 'multisystem' disease – carries a risk of a poor outcome, including 10–20% mortality and a 50% risk of life-impairing morbidity.

1. Clinical information on LCH in adults

LCH may affect any age group, from the newborn to the elderly. For several reasons the disease is more

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familiar to paediatricians than to adult physicians and so most of the available information about clinical features, pathogenesis, and treatment outcome derives from the paediatric experience. Only a few reports are available describing series of patients in whom LCH was diagnosed during adulthood. Furthermore, most reports are based on single-specialty experiences, which favour biased description of the patients. In 1964 for instance, Lewis reported 12 patients with 'eosinophilic granuloma and its variants with special reference to lung involvement' [4], whilst in 1991 Axiotis reviewed 42 cases of LCH involving the female genital tract, either as 'pure' genital LCH, genital LCH with subsequent multi-organ involvement, oral or cutaneous LCH with subsequent genital and multi-organ involvement, or diabetes insipidus with subsequent genital and multi-organ disease. Complete regression, partial improvement, persistent lesions, and recurrences were seen in all four groups of patients. Treatment was highly individualised and included surgery, irradiation, topical corticosteroids, topical nitrogen mustard, systemic chemotherapy, and combinations of these treatments. Although no modality was shown to yield a superior outcome, the authors, surprisingly, suggested complete surgical excision as initial therapy [5].

In 1995 Kilpatrick and colleagues, from the Mayo Clinic, reported the clinical and pathological features of 263 patients with LCH and bone involvement, including 91 adults, reviewed over an 80-year period. The most common presenting complaint was pain, often worse at night. The skull was the most frequent osseous site in children and adults. Follow-up times varied from 3 months to 50 years, but three adults died either directly or indirectly from LCH and one developed systemic amyloidosis. Recrudescence of LCH in children, but not in adults, strongly correlated with the development of diabetes insipidus [6].

In 1996 Malpas and Norton described 47 well-documented patients with LCH, with a slight female preponderance and with onset as late as the ninth decade. The skin was the commonest site of presentation, but pulmonary and bone involvement were also frequent. Patients with single-site disease fared best. The worst prognosis was seen in the elderly or those with organ 'dysfunction'. There was a high incidence of various associated cancers, which could precede, coincide with, or postdate the diagnosis of LCH [7].

In 1997 Baumgartner and colleagues reported 19 patients whose biopsies met the histopathological criteria for presumptive LCH and who were followed for 1.5–20 years (average 7.7 years). Skeletal lesions (16 patients), diffuse interstitial lung infiltrates (7 patients), and pituitary gland involvement with diabetes insipidus (4 patients) were the most common manifestations. Lesions of the skull and axial skeleton were associated with infiltration of adjacent soft tissues in 10 (61%) of 16 patients. Liver, lymph node, and bone marrow involvement were also noted. Localised (single-site) disease had a good prognosis, but multifocal and multisystem LCH had a more aggressive course. Bone lesions with adjacent soft tissue infiltration ($n = 20$) showed a >80% relapse rate, independent of the type of treatment. Pulmonary involvement caused greater morbidity than the 'single system', and systemic treatment yielded no convincing effect. In 3 patients with liver or bone marrow involvement, LCH showed a persistent, serious handicap. One patient died after acute myelomonocytic leukaemia developed 18 months after diagnosis, without preceding chemotherapy. Their conclusion was that, in adults, LCH was usually limited to a few organ systems, and multifocal LCH represents the more aggressive form with an unfavourable prognosis in patients with bone lesions spreading into the adjacent soft tissue and liver, or bone marrow involvement [8].

In 1999 Howarth and colleagues described 314 Mayo Clinic patients with histologically proven LCH, followed for a median time of 4 years, including patients up to 83 years old. Multisystem LCH was identified in 96 patients, 25 of whom (26%) had continuing 'active' disease after treatment. Single-bone LCH lesions were observed in 114, of whom 111 (97%) were alive and disease free after treatment. The commonest sites of osseous LCH were the skull and proximal femur. Of the 87 patients with 'single system' pulmonary involvement, only three were non-smokers. After treatment with corticosteroids (with or without cyclophosphamide or busulphan), 74 patients survived apparently disease free, but 10 patients died. Diabetes insipidus (DI) developed in 44 patients (14%) of whom 30 were alive, disease free after treatment, though all required long-term replacement therapy with desmopressin acetate. Lymph node involvement was found in 21 (16%) patients, and mucocutaneous involvement in 77 (24%) patients. Those with single-system bone lesions had the best prognosis compared with patients with LCH involving other systems. By contrast, 20% of patients with multisystem involvement had progressive disease, despite treatment [9].

In 2000 Kaltsas and colleagues described hypothalamo-pituitary abnormalities in 12 adults with LCH and DI, followed up for a median of 11.5 years. The median age at diagnosis of DI was 34 years; DI was the presenting symptom in 4 patients, whereas the other 18 adults developed DI within 1–20 years (median, 2 years) after the diagnosis of LCH. 8 patients developed one or more anterior pituitary hormonal deficiencies at a median of 4.5 years (range, 2–22 years) after the diagnosis of DI. All patients developed other sites of disease, outside the hypothalamus, during the course of the study and no fluctuation of disease activity in the hypothalamo-pituitary region was noted. Anterior pituitary hormone deficiencies developed in 8 of 12 patients

with hypothalamic LCH and DI, over the course of 20 years. Radiotherapy seemed to be useful in achieving local control of tumour extent but established anterior or posterior pituitary and hypothalamic dysfunction did not improve [10].

2. Pulmonary LCH: an intriguing problem

The high proportion of cases with pulmonary disease is the most striking difference between children and adults with LCH (see Table 1). Histologically, this form of the disease is characterised by granulomatous lesions containing 'LCH cells' that destroy distal bronchioles. Progress has been made in understanding the aetiology and pathogenesis of the disease and linkage to cigarette smoking has been noted for many years. Modifications in the bronchiolar epithelium induced by smoking, such as the increased secretion of granulocyte-macrophage-colony-stimulating factor by these cells, are probably responsible for the initial accumulation of large numbers of LC and in these cases of LCH cells. A potential role also for so-called passive smoke, i.e. the cigarette smoke unwillingly inhaled by children and adults surrounding cigarette smokers, remains to be assessed. However, given the rarity of pulmonary LCH compared with the frequency of smoking, an as yet unidentified genetic predisposition or one or more other 'acquired' factors may also be necessary for the development of the disease. Although LCH cells in LCH granulomas may be clonal in origin, several observations argue against the idea that the disease, which can regress spontaneously, is a malignant process. Cells of dendritic cell lineage (including LC) are potent antigen-presenting cells, suggesting that pulmonary LCH results from an uncontrolled immune response initiated by normal and abnormal LC. Consistent with this idea, LC and T-cells are the predominant populations found in the early lesions of pulmonary LCH and, unlike LC in the normal bronchial mucosa and those accumulating in other disease states, LCH cells in pulmonary LCH granulomas express surface molecules important for the activation of T-lymphocytes. A number of mediators are produced in the microenvironment of granulomas that probably influence the outcome of the local immune and inflammatory reaction. Ultimately, precise knowledge of the pathogenesis of this disorder should permit the development of specific treatment. In order to investigate the possible clonality of pulmonary LCH, Yousem and colleagues [11] used the X-linked polymorphic human androgen receptor assay (HUMARA) locus to assess clonality in female patients from whom one or more discrete LCH nodules had been removed at open lung biopsy. 'LCH cells' were excised from formalin-fixed, paraffin-embedded tissue by microdissection to assure a relatively pure cellular population, and studies for differential methylation patterns at the HUMARA locus were performed. Twenty-four nodules in 13 patients were evaluated. Seven (29%) were clonal and 17 (71%) were non-clonal. Of six cases with multiple discrete nodules, three (50%) showed a non-clonal 'LCH cell' population. In one biopsy with five nodules, two nodules were clonal with one allele inactivated, one nodule was clonal with the other allele inactivated, and two nodules were non-clonal. Thus, pulmonary LCH appears to be primarily a reactive process in which non-lethal, non-malignant clonal evolution of LCH cells may arise in the setting of non-clonal LCH cell hyperplasia. Cigarette smoking may be the stimulus for pulmonary LCH, in contrast to other forms of LCH.

Why do 'LCH cells' accumulate in the lung in patients with LCH? Whether or not the accumulation of large numbers of LCs in the course of the disease depends on their proliferation or prolonged survival, or both, is still controversial. In 1998 Brabencova and colleagues [12] reported their study of the proportion of LCs replicating in biopsied granulomas from both localised and diffuse form of LCH, using several histopathological techniques used for assessment of cell proliferation. They found that, except for proliferating cell nuclear antigen, all parameters measured were low in all forms of the disease. They were clearly less than those of most neoplastic cells and similar to those of renewing epithelial cells. They concluded that the 'LCH cells' in LCH granulomas are not a rapidly dividing cell population and that local replication makes a minimal contribution to granuloma maintenance. However, these data are apparently at variance with more recent data on the expression of cell cycle-related gene products in 30 different cases of LCH. In all those cases, there was scattered nuclear-positive staining for the proliferation marker Ki-67, indicating that in LCH the LCH cells are proliferating. In >90% of the cases, expression of transforming growth factor-β receptors I and II, MDM2, p53, p21, p16, Rb, and Bcl2 was detected in lesional LCH cells. The over-expression varied from limited focal staining of scattered cells within the lesion to strong diffuse staining, but the findings suggest that the cellular mechanisms sensing and responding to

Table 1
Summary of similarities and differences between adult and childhood LCH

Manifestation	Adult	Childhood
Bone disease	Frequent	Extremely frequent
Skin disease	Frequent	Frequent
Dental involvement	Frequent	Infrequent
Pulmonary disease	Very frequent	Infrequent
Pulmonary isolated disease	Very frequent	Exceptional
Genital involvement	Frequent	Exceptional
Diabetes insipidus	Frequent	Frequent

DNA damage, namely the p53-p21 pathway and the p16-Rb pathway, are activated. Conversely, over-expression of Bcl2 may play a part in the activation of p53 and p16 and/or the arrest of apoptosis. These data suggest that in LCH the cell-cycle lesion is 'hyperactive' and that there is an imbalance between proliferation and apoptosis [13].

3. What is the standard treatment of LCH in adults?

The uncertainties concerning the pathogenesis of LCH have certainly limited rational treatment options. Furthermore, compared to children, only limited information is available for adult patients. In 1992 Tsele and colleagues reported their evaluation of 3 adult patients with severe or resistant LCH (one single-system skin disease, two with multisystem disease), treated with etoposide, 100 mg/m^2/day, for 3 days, repeated every 3 or 4 weeks for 3–4 cycles. All patients achieved clinical remission for 12–14 months of follow up. No serious immediate side-effects were noted [14].

In 1997 Giona and colleagues reported a retrospective single-centre study of 11 adults with LCH. Of 6 patients with recurrent unifocal ($n = 3$) or multifocal ($n = 3$) bone disease, five received also chemotherapy with vinblastine VBL and high-dose methylprednisolone (HDMP) and one received α-interferon; of 4 patients with multisystem disease, two with bone and visceral disease were treated with etoposide and + HDMP and two with lung and lymph node involvement received multi-agent chemotherapy, with good results [15].

Saven and Burian conducted a phase II trial of cladribine (2-CDA) in 13 adults with LCH at the Scripps Clinic. Seven patients had cutaneous involvement, six multifocal osseous, six pulmonary, two had additional soft tissue and nodal involvement, and four had diabetes insipidus. After a median of three courses, 7 (58%) patients achieved complete responses and two partial responses, an overall response rate of 75%. Seven patients experienced grade 3 to 4 neutropenia. Median response follow-up duration was 33 months (range, 1–65 months). At a median follow-up of 42 months (range, 5–76 months), 12 patients remained alive and one had died. The authors concluded that cladribine has major activity in adult LCH and warrants further investigation as a single agent and in combination with other drugs [16].

Even though it is the commonest form of the disease in adults, the treatment of 'isolated' pulmonary LCH is even less well defined. In their review of 100 cases of 'eosinophilic granuloma' diagnosed by open lung biopsy, Friedman and colleagues reported that outcome was 'generally benign' in the 60 cases in which clinical follow-up information was obtained. All 16 asymptomatic patients remained well; 17 others had complete remission of symptoms, 22 had persistent symptoms though half had partial improvement; 4 patients had progressive disease despite treatment, but only 1 patient died (of bilateral pneumothoraces complicating severe fibrosis). The more severe manifestations were found in young males, who had a higher incidence of pneumothorax, fibrosis and honeycombing, and also DI. The effectiveness of treatment with corticosteroids could not be assessed because there was no control group; some individuals appeared to benefit, but relapse was very unusual. The observation that smoking was far more common among these patients (97% altogether) than in the general population (about 35%) was considered, at that time, an unexplained finding [17].

Recurrent reports of improvement or even spontaneous resolution following smoking cessation [18] have supported the concept that pulmonary LCH is a mild disorder that does not require an aggressive treatment. Furthermore, the concept that this is an inflammatory disease provided support to the empirical use of steroids, either in short pulses or longer exposure.

Recently, Vassallo and colleagues reviewed the records of 102 adults with histopathologically confirmed pulmonary LCH to ascertain their current vital status and whether cancer had been diagnosed. After a median follow-up period of 4 years (range, 0–23 years) there were 33 deaths, 15 of which were attributable to respiratory failure. Six haematological cancers were diagnosed. The overall median survival was 12.5 years, which was significantly shorter than that expected for persons of the same sex and calendar year of birth ($P < 0.001$). In a univariate analysis, variables predictive of shorter survival included an older age ($P = 0.003$), a lower forced expiratory volume in 1 s (FEV_1) ($P = 0.004$), a higher residual lung volume ($P = 0.007$), a lower ratio of FEV_1 to forced vital capacity ($P = 0.03$), and reduced carbon monoxide diffusing capacity ($P = 0.001$) [19].

Since respiratory failure is a limiting factor for both survival and quality of life of patients with pulmonary LCH, lung transplantation has been employed both in children and in adults with advanced disease and limited pulmonary function. Although this has provided some benefit to some patients with limited pulmonary function, failures are reported due to local recurrence of LCH after transplantation [20].

4. Treatment of LCH in adults: where do we go from here?

Since the 1960s, a number of small, single- and multicentre studies for children with multisystem LCH have shown a clear benefit from therapy with cytotoxic drugs and/or steroids, either alone or in combination. On the basis of these preliminary findings, an international cooperative effort by the Histiocyte Society, including two randomised trials [21–23], has produced a considerable

amount of information about LCH in childhood and the response to therapy. Much of this information may reasonably be transferred from children to adult patients, though this cannot be taken for granted. The International Histiocyte Society Registry was the first step toward a cooperative effort in LCH of adults [24]. Of >250 patients registered, single-system disease was found in 86 (31%), included pulmonary involvement only in 44 cases, while 188 patients (69%) had multisystem disease. The data collected support the great uncertainty and the lack of a therapeutic standard at least for front-line treatment, and further support the need for a common approach in a prospective, cooperative trial. To be able to address this issue, several requirements still have to be achieved. Uniform initial evaluation and stratification of patients is necessary for the evaluation of the course and of treatment results for a disease in which, on the one hand, spontaneous resolution and improvement, on the other, reactivation are common. Furthermore, the aims of the study should be appropriate for the different patient groups. For example, most patients with localised disease are not at risk for disease-related death. Patients with isolated pulmonary disease are an exception: thus, their treatment should aim at a reduction of the frequency and severity of reactivations, with the intent of reducing the degree of eventual disability. This might result in an improved quality of life. Multisystem LCH is associated, in adults as in children, with a 10% risk of fatal disease progression at 5 years [23]. Systemic chemotherapy may reduce the proportion of these failures. The therapeutic efficacy of the standard regimen for multisystem LCH in children, i.e. the combination of vinblastine + prednisone, should thus be explored in adult patients.

For patients with 'isolated' pulmonary LCH, the 5-year probability of survival is around 80% [24]. Given the specific characteristics of this disease, and the frequent occurrence of mild cases with sustained spontaneous regression or stabilisation, we still need to describe the natural history of the disease and, in particular, the impact of smoking cessation on the disease course. Although widely used, the efficacy of steroid monotherapy in such patients has not yet been assessed objectively. Furthermore, in patients with disease progression on corticosteroids it seems logical to assay the therapeutic efficacy of standard chemotherapy (vinblastine + prednisone), as for patients with multisystem disease. Although the results obtained in multisystem children are promising, incomplete knowledge of the pathogenesis of the condition suggests caution in extending such an indication as a direct extrapolation to pulmonary LCH in adults. Furthermore, in adult patients, additional features have to be considered, among them the possibility that the patient may have associated, pre-existing conditions that may affect disease manifestations and drug metabolism; in adults with diabetes mellitus, for example, glucose intolerance may require modification of steroid dosage; autoimmune disorders may require immune modulation; pregnancy may affect the immune system and thus both the disease course and its treatment; and there is an increased risk of malignancies in adults with LCH.

On the basis of these considerations, the Histiocyte Society has launched the first international cooperative trial for the diagnosis and treatment of LCH in adults. This trial, known as LCH-A1, is aimed at: defining and implementing the uniform initial evaluation and stratification of patients; defining a common therapeutic strategy for patients with (a) multisystem and (b) pulmonary LCH; exploring the therapeutic efficacy in adult patients of the standard regimen (vinblastine + prednisone) for multisystem LCH in children; defining the natural history of 'isolated' pulmonary disease and in particular the role of smoking cessation on the disease course; and exploring the efficacy of steroid monotherapy in adults with isolated pulmonary disease and disease progression. The results of this study will no doubt contribute to a better understanding of the characteristics of LCH in adults and to help to establish the first 'therapeutic standard' for this intriguing disease. Participation in this trial by national cooperative groups and large institutions is encouraged. Details of the LCH-A1 trial and copies of the literature, including patient information sheets, are available from the author.

5. Conclusion

LCH in adults is still considered to be an 'orphan disease', about which our knowledge is certainly incomplete. The Histiocyte Society is trying to transfer to this group of patients the experience it has gathered in children. The Society's LCH-A1 trial also offers a unique opportunity for research, since beside the uncertainties about treatment, investigators still have many unanswered questions concerning the epidemiology and aetiopathogenesis of the disease.

Is LCH in adults a clonal disease of LCH cells? The observation of clonality in LCH cases challenged this concept but still remains controversial [25,26]. Accumulation of a library of tissues from patients with different, well-defined disease manifestations might provide hints for research in this field.

Is LCH a genetic disease? The observation that around 1% of cases of LCH have another affected relative, either child or adult, strongly suggests a genetic predisposing factor [27,28]. Furthermore, evidence of chromosomal abnormalities found in phytohaemagglutinin-stimulated peripheral blood lymphocytes of LCH patients at diagnosis, during the disease course and during long-term follow up – more frequently in patients

with multisystem disease – suggests that chromosomal instability may be part of LCH [29]. The association between LCH and cancer, well defined in children [30], needs further investigation in adult patients.

Is pulmonary 'isolated' LCH a reactive disease triggered by cigarette smoking? The role of cigarette smoking appears very convincing in many cases. Yet we still need further information on both the negative impact of cigarette smoking in patients who develop the disease (including correlation with number of cigarette/year) and the possible contribution to treatment by documented smoking withdrawal. This can only be achieved in a prospective trial aiming also to address this specific issue. Furthermore, patients with different responses to cigarette smoke exposure might be investigated for underlying genetic heterogeneity.

Is LCH another form of selective immune deficiency? There is increasing evidence that dysregulation of cellular mechanisms related to the immune response may result in 'unexpected' phenotypes [31,32]. Extensive functional assessment, as well as an evaluation of genetic polymorphism of some putative molecules and genes might provide new insights. Recent evidence that there is no gross functional abnormality in dendritic cells (LC) generated from the circulating monocytes of patients with LCH makes it unlikely that LCH is due to a severe functional defect, but a subtle or more selective abnormality is still possible [33]. A constitutional defect in T-lymphocyte function might provide an explanation for pathogenesis of LCH, at least in a subset of patients.

These and other new hypotheses to be developed during the study will be investigated by ancillary studies within the framework of LCH-A1. A joint effort between scientists, paediatricians and adult specialists could provide the catalyst for progress that is now required so that the aetiology, pathogenesis and rational management of this puzzling disorder can eventually be identified.

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References

1. Arceci RJ. The histiocytoses: the fall of the Tower of Babel. *Eur J Cancer* 1999, **35**, 747–767.
2. Lampert F. Langerhans cell histiocytosis. Historical perspectives. *Hematol Oncol Clin North Am* 1998, **12**, 213–219.
3. Aricò M, Egeler M. Clinical aspects of Langerhans cell histiocytosis. *Hematol Oncol Clin N Am* 1998, **12**, 247–258.
4. Lewis JG. Eosinophilic granuloma and its variants with special reference to lung involvement. *QJM New series* 1964, **XXIIII**, 337–359.
5. Axiotis CA, Merino MJ, Duray PH. Langerhans cell histiocytosis of the female genital tract. *Cancer* 1991, **67**, 1650–1660.
6. 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.
7. Malpas JS, Norton AJ. Langerhans cell histiocytosis in the adult. *Med Pediatr Oncol* 1996, **27**, 540–546.
8. Baumgartner I, von Hochstetter A, Baumert B, Luetolf U, Follath F. Langerhans'-cell histiocytosis in adults. *Med Pediatr Oncol* 1997, **28**, 9–14.
9. Howarth DM, Gilchrist GS, Mullan BP, Wiseman GA, Edmonson JH, Schomberg PJ. Langerhans cell histiocytosis: diagnosis, natural history, management, and outcome. *Cancer* 1999, **85**, 2278–2290.
10. 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 Endocrinol Metab* 2000, **85**, 1370–1376.
11. Yousem SA, Colby TV, Chen YY, Chen WG, Weiss LM. Pulmonary Langerhans' cell histiocytosis: molecular analysis of clonality. *Am J Surg Pathol* 2001, **25**, 630–636.
12. Brabencova E, Tazi A, Lorenzato M, *et al*. Langerhans cells in Langerhans cell granulomatosis are not actively proliferating cells. *Am J Pathol* 1998, **152**, 1143–1149.
13. Schouten B, Egeler RM, Leenen PJ, Taminiau AH, Van Den Broek LJ, Hogendoorn PC. Expression of cell cycle-related gene products in langerhans cell histiocytosis. *J Pediatr Hematol Oncol* 2002, **24**, 727–732.
14. Tsele E, Thomas DM, Chu AC. Treatment of adult Langerhans cell histiocytosis with etoposide. *J Am Acad Dermatol* 1992, **27**, 61–64.
15. Giona F, Caruso R, Testi AM, *et al*. Langerhans' cell histiocytosis in adults: a clinical and therapeutic analysis of 11 patients from a single institution. *Cancer* 1997, **80**, 1786–1791.
16. Saven A, Burian C. Cladribine activity in adult Langerhans-cell histiocytosis. *Blood* 1999, **93**, 4125–4130.
17. Friedman PJ, Liebow AA, Sokoloff J. Eosinophilic granuloma of lung: clinical aspects of primary histiocytosis in the adult. *Medicine (Baltimore)* 1981, **60**, 385–396.
18. Mogulkoc N, Veral A, Bishop PW, Bayindir U, Pickering CA, Egan JJ. Pulmonary Langerhans' cell histiocytosis: radiologic resolution following smoking cessation. *Chest* 1999, **115**, 1452–1455.
19. Vassallo R, Ryu JH, Schroeder DR, Decker PA, Limper AH. Clinical outcomes of pulmonary Langerhans'-cell histiocytosis in adults. *N Engl J Med* 2002, **346**, 484–490.
20. Gabbay E, Dark JH, Ashcroft T, *et al*. Recurrence of Langerhans' cell granulomatosis following lung transplantation. *Thorax* 1998, **53**, 326–327.
21. Ladisch S, Gadner H. Treatment of Langerhans cell histiocytosis – evolution and current approaches. *Br J Cancer Suppl* 1994, **23**, S41–S46.
22. Gadner H, Grois N, Arico M, *et al*. A randomized trial of treatment for multisystem Langerhans' cell histiocytosis. *J Pediatr* 2001, **138**, 728–734.
23. Minkov M, Grois N, Aricò M, *et al*. Preliminary results of the LCH-II clinical trial of the Histiocyte Society. Proceedings of the SIOP XXXV meeting. *Medical Pediatr Oncol* 2003, **41**, 263.
24. Aricò M, Girschikofsky M, Généreau T, *et al*. Langerhans cell histiocytosis in adults. Report from the International Registry of the Histiocyte Society. *Eur J Cancer* 2003, **39**, 2341–2348.
25. Willman CL, Busque L, Griffith BB, *et al*. Langerhans'-cell histiocytosis (histiocytosis X) – a clonal proliferative disease. *N Engl J Med* 1994, **331**, 154–160.
26. Willman CL, McClain KL. An update on clonality, cytokines, and viral etiology in Langerhans cell histiocytosis. *Hematol Oncol Clin North Am* 1998, **12**, 407–416.

27. Aricò M, Danesino C. Langerhans' cell histiocytosis: is there a role for genetics? *Haematologica* 2001, **86**, 1009–1014.
28. Aricò M, Nichols K, Whitlock JA, *et al*. Familial clustering of Langerhans cell histiocytosis. *Br J Haematol* 1999, **107**, 883–888.
29. Scappaticci S, Danesino C, Rossi E, *et al*. for the AIEOP-Istiocitosi Group, Cytogenetic abnormalities in PHA-stimulated lymphocytes from patients with Langerhans cell histiocytosis. *Brit J Haematol* 2000, **111**, 258–262.
30. Egeler RM, Neglia JP, Arico M, *et al*. The relation of Langerhans cell histiocytosis to acute leukemia, lymphomas, and other solid tumors. The LCH-Malignancy Study Group of the Histiocyte Society. *Hematol Oncol Clin North Am* 1998, **12**, 369–378.
31. Arico M, Imashuku S, Clementi R, *et al*. Hemophagocytic lymphohistiocytosis due to germline mutations in SH2D1A, the X-linked lymphoproliferative disease gene. *Blood* 2001, **97**, 1131–1133.
32. Grimbacher B, Holland SM, Gallin JI, *et al*. Hyper-IgE syndrome with recurrent infections–an autosomal dominant multisystem disorder. *N Engl J Med* 1999, **340**, 692–702.
33. Holter W, Ressmann G, Grois N, Lehner M, Parolini O, Gadner H. Normal monocyte-derived dendritic cell function in patients with Langerhans-cell-histiocytosis. *Med Pediatr Oncol* 2002, **39**, 181–186.