Langerhans cell histiocytosis: old disease new treatment

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Summary

Langerhans cell histiocytosis (LCH) has been previously thought of as a rare illness, but is now increasingly diagnosed as a result of the more intensive investigations of patients with cystic pulmonary disease. In recent years, treatments developed from our new understanding of the molecular biology of malignant disease have been applied to patients with LCH, and responses seen. In this review, we describe the origins, presentation and modern treatment of LCH, showing that there is new hope for patients with this condition.

Introduction

Langerhans cell histiocytosis (LCH) is a rare clonal proliferative disease characterized by the infiltration of a single organ or multiple organs by cells phenotypically similar to Langerhans cells (LCs). LCH encompasses a spectrum of disorders with diverse clinical presentations ranging from single organ to multiple organ involvement. This heterogeneous nature of the condition led to a number of eponymous descriptions of the multisystem (MS) forms of LCH such as Letterer–Siwe disease, Hand–Schüller–Christian disease and systemic histiocytosis X, while localized disease is prosaically described as ‘eosinophilic granuloma’.

The aetiology and pathology of LCH remain unknown and the condition is rare. It is difficult to value treatment regimens as the disease is so uncommon. Our attempts to define treatment are based on anecdotal reports and clinical trials of very small numbers of patients. This review collates recent advances in our understanding of the pathology, and management of LCH, with particular attention to the adult pulmonary form of this disease.

LCs, their origins and function

The skin and mucous membranes are the body’s first line of defence against pathogens. Specific cells within the skin and mucous membranes have evolved to initiate and regulate the immune response. These cells, the dendritic cells, are divided into LCs located in epidermis and interstitial dendritic cells, which are sited in mucous membranes and dermis.

Paul Langerhans, a German medical student, first described LCs in 1868. Langerhans believed that LCs functioned as intra-epidermal receptors for the nervous system. We now know that LCs are antigen-presenting cells, which express surface glycoproteins such as CD1a and langerin, both of which are related to the major histocompatibility complex (MHC) Class 1 and 2, respectively. LCs are involved in the activation of CD4+ lymphocytes, and the process of macrophagocytosis of pathogens. LCs are characterized by the presence of Birbeck granules, which are cytoplasmic rod-shaped organelles believed to be important in antigen internalization, and seen only by electron microscopy. Following antigenic activation, LCs migrate to lymph nodes, and there they stimulate naïve
T cells to secrete cytokines, such as GM-CSF, IL-15, Tumour necrosis factor-alpha (TNF-α) and TGF-β, launching an immune response. LCs can repopulate in the epidermis by either local proliferation or by maturation of monocyte-macrophage lineage.3

**LCH**

LCH cells and LCs express similarities such as the presence of Birbeck granule.4 However, differences include a more rounded appearance and lack dendritic cell extensions in LCH cells microscopically. Advances in immunology and molecular biology have enhanced our ability to compare differences at the molecular level. LCH cells express CD1a, Langerin and S100, but fail to express markers typical of a more mature dendritic cell such as CD83.

LCH is thought to have an incidence in adults of 1–2 per million population,5 and in children of 2–10 cases per million,6,7 but these figures are likely to underestimate the incidence of the disease. LCH can, in many ways, be considered a malignant process because it is a clonal proliferation.8,9 However, some consider LCH to be a reactive condition, where there is an aberrant reaction between T lymphocytes and LCs secondary to immature dysregulation.10

**Presentation and classification**

LCH encompasses a group of disorders characterized by tissue infiltration with LC granulomas. The clinical presentation is variable, depending on the affected organ. Patients classically present with a gamut of symptoms depending on the site of the granuloma. Symptoms may include pain or fracture from an osteolytic lesion.

The Histiocyte Society has made a major contribution to the management of LCH. The society has categorized LCH into two major groups (Tables 1 and 2), with significantly different prognoses, to help with treatment and diagnosis.1 Since LCH is more common in the paediatric population, most of the clinical trials have been carried out on this population. However, children cannot be simplified as ‘small adults’ as factors such as pharmacokinetics differ. Therefore, paediatric treatment regimens for LCH cannot simply be extrapolated to the adult population. The treatments mentioned in this review were conducted in the paediatric population unless specified otherwise.

### Table 1 Single-system LCH

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<table>
<thead>
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<tbody>
<tr>
<td>A</td>
<td>Single site (unifocal lymph node, skin, lung, pituitary or bone)</td>
</tr>
<tr>
<td>B</td>
<td>Multifocal disease (multifocal bone or multiple nodes)</td>
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### Table 2 MS LCH

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<tr>
<td>A</td>
<td>Two or more organs involved at diagnosis without organ dysfunction.</td>
</tr>
<tr>
<td>B</td>
<td>Two or more organs involved at diagnosis with evidence of organ dysfunction.</td>
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</table>

(i) High risk: high mortality rate with involvement of one or more of risk organs (liver, lungs, spleen or haematopoetic system).11

(ii) Low risk: excellent prognosis, involvement of other organs.11

**Single-system LCH**

With the exception of pulmonary LCH, single-system LCH has an excellent prognosis with a high incidence of spontaneous remission. However, there may be significant morbidity from fractures or skin disfigurement, and treatment needs to be tailored for each individual patient.

**Skin**

An eczematous rash is the typical manifestation of cutaneous LCH. Fifty percent of skin LCH regresses within a few months, but can reactivate and progress to a disseminated fatal form.12 Isolated skin nodules can be surgically excised or may be relieved by topical emollients. Severe LCH skin can be treated with either short periods of psoralen with ultraviolet (PUVA) photochemotherapy or with topical nitrogen mustard.12,13 Topical steroids, ciclosporin and tacrolimus have been used anecdotally with varying success.

In the adult population, treatment with surgery, topical steroids, topical nitrogen mustard, PUVA, intravenous interferon, radiotherapy, vinblastine with or without steroids, etoposide, thalidomide and isoretinoin have been reported.14–17

**Bone**

Bone is the most common organ affected by LCH and has a good survival rate, as osseous lesions can spontaneously heal. Children often present with a single skull lesion,18 where bone lesions do not look likely to fracture, or cause compressive symptoms, observation is a management option. Bone
lesions may critically affect other organs, but this is very unusual. Spinal cord compression is rarely seen and is treated with steroids and low-dose radiation therapy. Surgical resection is not advised, but biopsies or curettage seem to have magical effects and can lead to healing.19

A variety of treatments have been used in bone-only LCH. Munn et al.20 identified high levels of prostaglandin E2 in bony lesions and reported a good response to Indomethacin in adults. Bisphosphonates have been used as pain relief and may control disease progression, possibly by inhibiting osteoclast activity or acting to reduce local cytokine expression.21–25 Furthermore, surgical curettage, corticosteroid injections, corticosteroids with or without vinblastine and irradiation have been used in the adult population.26–28

Central nervous system

Patients with central nervous system (CNS) LCH will have clinical features related to the site of the lesion. Cladribine has been reported to provide four partial and eight complete radiographic responses in 12 patients with CNS mass lesions.29 Treatments used have included intravenous immunoglobulin, either in combination with chemotherapy30 or with trans-retinoic acid,31 but results have been mixed. Burn et al. have reported dramatic clinical and radiological response to Etoposide in the treatment of two cases of LCH with CNS involvement.32

Isolated diabetes insipidus

The differential diagnosis of diabetes insipidus classically includes LCH. Although cladribine may occasionally reverse diabetes insipidus,33 the enormous majority of patients will have irreversible diabetes insipidus. Radiotherapy has been used as an option in the adult population.34 Although the current recommendation is to treat recent-onset diabetes insipidus secondary to LCH to prevent progression, the exact regimen to be used remains undefined.

Pulmonary LCH

Pulmonary LCH is a rare interstitial lung disease. Information about the natural history of the disease, and in particular its duration, is unavailable as patients can be asymptomatic for significant periods before coming to diagnosis and because the condition can spontaneously remit.

The clinical symptoms of pulmonary LCH can present at any age and may be part of a single-system LCH or as MS LCH. In children and infants, the pulmonary form of the disease before coming to diagnosis commonly occurs as part of a MS LCH. In contrast, the isolated pulmonary form occurs mainly in young adults between the ages of 20 and 40 years.35–41

Pathology, aetiology and presentation

The pathology of pulmonary LCH is poorly understood, but granulomas rich in LCs, eosinophils, macrophages and lymphocytes develop in and destroy distal bronchioles as a result of a cell-mediated immune response. The lesions are focal, poorly demarcated, separated by apparently normal lung parenchyma and centred on the terminal and respiratory bronchioles destroying the airway walls.

A total of 90–100% of patients with pulmonary LCH are cigarette smokers.35–42 This observation led to the hypothesis that cigarette smoking may have a role in the pathogenesis of LCH, possibly by mediating changes in the bronchiole microenvironment. Lung fibrosis may be promoted by the activation of lung fibroblasts via bombesin-like peptides, which are secreted from neuroendocrine cells in response to cigarette smoking.43 The cigarette component tobacco glycoprotein is a potent immunostimulant and can inhibit cytokine production such as IL-2.44,45 IL-2 inhibits the differentiation of histiocytes, and therefore, a lack of IL-2 may promote histiocyte differentiation. Tobacco antigens may induce circulating antibody complexes and cause pulmonary change as a result.46

Pulmonary LCH may be asymptomatic in up to a quarter of patients and diagnosed as an incidental finding following a chest X-ray.36,37,39 The signs of lung damage seen on X-ray may be out of proportion to the patients’ with relatively minor symptoms. Respiratory symptoms such as dry cough, dyspnoea on exertion are the most common symptoms, but constitutive symptoms such as weight loss, fever and night sweats may also be present.36,37,39 Less commonly, patients may present with spontaneous pneumothoraces, wheezing, pleuritic chest pain and, rarely, with haemoptysis.36,39

Treatment

Initial therapy. LCH treatment is not standardized, and based on anecdote. A strategy for the management of this disease needs to be developed. As a primary step in any treatment strategy, cigarette-smoking cessation is advised and, as a result, clinical and radiographic improvement occasionally reported.47–49

Failure of preventing disease progression by smoking cessation is generally followed by steroid treatment. Steroids are widely used despite limited data supporting their efficacy. Schonfeld et al.38...
reported to improve constitutional symptoms and radiological findings, but without effect on lung function.

Disease progression after 6 months’ treatment with steroids is generally followed by chemotherapy. The agents used include vinblastine and mercaptopurine or, more recently, single agent cladribine, which will be reviewed here in more detail.

**Lung transplantation.** Pulmonary LCH patients can progress to severe respiratory impairment and end-stage pulmonary disease. In these patients, lung transplant should be considered. Pulmonary LCH may recur in the transplanted lungs; therefore, it is essential to ensure that the disease has been eradicated prior to referral for a lung transplant. Early referral of pulmonary LCH patients to transplant centres is recommended.

**MS LCH**

During the 1960s through to the 1980s chemotherapy was used to treat LCH, and this was based on the belief that LCH was a malignant process. Single agents such as etoposide, methotrexate, 6-mercaptopurine, vinblastine and vincristine were initially used in paediatric patients and found, anecdotally, to be effective. These observations formed the basis of the rationale for two large prospective multicentre trials that used combination chemotherapy in MS LCH patients. These two studies showed that, although combinations of agents such as vinblastine and etoposide with prednisolone led to a good response rate of 60–90%, there was no overall beneficial effect on mortality rate, and a high incidence of relapse. International prospective randomized trials by the Histiocyte Society have been conducted in the paediatric population since the 1990s with the aim of reducing mortality and relapse rates. The LCH-I trial compared the effectiveness of a 6-month course of either vinblastine or etoposide in combination with prednisolone in children, and concluded that there was no significant difference in survival, response, reactivation or long-term sequelae with either treatment. This study made the important observation that no response at after 6 weeks of treatment defines a poor prognosis, with an associated mortality rate of up to 66%. The LCH-II trial compared the benefits of the addition of etoposide to vinblastine, prednisolone and mercaptopurine in high-risk MS paediatric LCH patients. The LCH-II trial showed that more intensive treatment does increase response rates and reduces mortality from LCH.

The Histiocyte Society’s current trial, LCH-III, has been planned in order to assess whether the addition of methotrexate to prednisolone and vinblastine and increasing the treatment duration to 12 months will reduce relapse rates. The results are awaited.

Prior to 2004, the majority of trials were conducted in children. With little data on the adult form of the disease, the LCH Adult-I trial was started in 2004 and assesses the value of vinblastine and prednisolone with mercaptopurine as first-line therapy, and second-line treatment with cladribine.

**Refractory LCH**

MS-LCH patients who are refractory to treatment and who relapse have a poor outcome with conventional treatment. There is no current standard salvage regimen, and chemotherapy agents such as vinblastine, methotrexate, etoposide and cyclophosphamide have been used to little effect. Most recently, cladribine has been used as second-line treatment in resistant cases of all types of LCH, with response rates ranging from 64% to 100% in children and adults (Table 3), and this has transformed the management of LCH. However, standardized treatment dosage and length need to be developed. The use of this agent and its apparent success has led to considerable hope for cladribine, and even more for patients affected by LCH.

Cladribine is a purine nucleoside analogue with selective toxicity to lymphocytes and monocytes, acting by interfering with single-stranded DNA repair and synthesis in both resting and dividing lymphocytes and monocytes. Saven et al. were the first to publish results of the efficacy of cladribine in LCH describing a complete response in three patients. Cladribine has been combined with cytarabine in childhood refractory LCH and combination therapy may be of benefit in patients with high-risk refractory disease, although toxicity may be a limiting factor. Cladribine has been combined with cytarabine in childhood refractory LCH and combination therapy may be of benefit in patients with high-risk refractory disease, although toxicity may be a limiting factor.
New therapies for LCH

Over the past decade, research has been based more on anecdotes than on science because of the limits imposed by the rarity of LCH. Reports are confined to case studies and small groups of patients, but nevertheless are, despite the anecdotal, of interest. The costs of treatment are relatively limited and, for the most expensive of all of the agents, do not exceed £1000 a course. Therapy can usually be given as outpatient treatment, further limiting costs.

**Clofarabine**

Clofarabine is a deoxyadenosine analogue, which has shown significant single-agent activity in patients who have failed or are resistant to conventional treatment, including cladribine.63

**Thalidomide**

Because cytokines have an important role in the pathogenesis of LCH, it has been thought that targeting the chemokine-receptor axis may provide new therapeutic targets, and this has been the theoretical basis for studies of TNF-α inhibition.

Thalidomide decreases TNF-α levels by affecting the TNF-α gene-promoter region. McClain et al.64 have described a phase II trial in patients who had failed primary and at least one secondary treatment.64 Ten of the 16 patients were classified as low-risk and 6 as high-risk patients. No high-risk patients responded, whereas there were seven responses in the low-risk group. The results suggest that thalidomide may have a role in treating low-risk patients with refractory skin and bone disease. This study has also opened the door to trials of other anti-TNF therapies, and there is a single report of the role of etanercept, a TNF-α inhibitor, in a child with non-responsive LCH.65

**Acitretin**

A good response has been reported in a patient with oral acitretin, which is a Vitamin A analogue, in a 57-year-old man with resistant cutaneous lesions.66 The patient also had retroperitoneal fibrosis, which improved after treatment with acitretin. The authors suggested a possible immuno-modulatory role of acitretin. Acitretin may provide an option for the treatment of patients with the less aggressive forms of LCH unsuitable for systemic chemotherapy.

**MACOP-B**

The MACOP-B chemotherapy regimen is used for Non-Hodgkin’s lymphoma and consists of a combination of prednisolone, vincristine, bleomycin, methotrexate, doxorubicin and cyclophosphamide. In 2009, Derenzini et al. reported a 100% response rate in seven adult patients treated with MACOP-B;67 three patients within this group of seven suffered from MS LCH and four had single-system LCH. There were two partial and five complete responses with three recurrences after stopping therapy.

**Cyclophosphamide**

The successful treatment of cutaneous and lymph node LCH with cyclophosphamide has been described in an adult patient who was disease-free at 3.5 year follow-up post-treatment and had not

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**Table 3** Review of cladribine treatment outcomes

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<tr>
<th>Authors</th>
<th>No. of patients</th>
<th>Response</th>
<th>Remission</th>
</tr>
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<tbody>
<tr>
<td>Saven et al. 199957</td>
<td>13</td>
<td>Overall response rate of 75%, with 58% complete and 17% partial responses.</td>
<td>Range 1–65 months</td>
</tr>
<tr>
<td>Grau et al. 200158</td>
<td>9</td>
<td>Overall response rate of 66% with 22% complete and 44% partial responses.</td>
<td>Range 2–12 months</td>
</tr>
<tr>
<td>Pardanani et al. 200359</td>
<td>5</td>
<td>100% overall response rate with 60% complete and 40% partial responses.</td>
<td>Remission ≤22 months.</td>
</tr>
<tr>
<td>Mottl et al. 200660</td>
<td>13</td>
<td>100% overall response rate with 70% complete response. The remainder 30% of patients achieved complete response with additional chemotherapy with or without irradiation.</td>
<td>Range 7 months to 8 years</td>
</tr>
<tr>
<td>Imamura et al. 201056</td>
<td>17</td>
<td>Overall response of 64%. 12 patients treated with cladribine monotherapy with 8 achieving complete response (66%).</td>
<td>Cladribine Monotherapy: Range 7–25 months.</td>
</tr>
</tbody>
</table>
responded to steroids and had relapsed after an initial response to narrow band UV (UVB) and PUVA.

Conclusion

The Histioocyte Society has significantly contributed to changes in the management of LCH. The society has done so by defining and classifying the different components of LCH and by simulating inception of clinical trials.

LCH is, in many ways, a malignant process, and it is of interest that the treatment of this condition, which used to be within the hands of the oncologists, who would treat with steroids and radiotherapy, is now returned to their care with the development of new, more intensive, treatment programmes.

The future for LCH patients looks brighter because of the development of new, active treatment regimens. There is a need to concentrate the treatment of this condition in specialist centres because the management has become increasingly multidisciplinary, requiring input from oncologists, dermatologists, endocrinologists, respiratory physicians and transplant surgeons.

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References


Langerhans Cell Histiocytosis


