Langerhans' Cell Histiocytosis

Definition[1]

Langerhans' cell histiocytosis (LCH) is one of the 'histiocytosis disorders', as defined by the Histiocyte Society. LCH is an abnormal proliferation and dissemination of clonal Langerhans' cells in which they accumulate, along with other inflammatory cells, and form tissue granulomas in different organs. It is named after the appearance of the cells, which resemble the normal dendritic cells found in the epidermis first noted by Langerhans. Although once considered a disorder of immune regulation, it is now described as a dendritic cell neoplasm with a strong inflammatory component[2].

It was formerly considered as a disease of childhood but is now recognised as often presenting in adulthood.

The clinical manifestations of LCH are very variable, ranging from self-resolving single-organ disease to a disseminated, aggressive disease with a 10-20% mortality[3]. LCH may affect one or many organs. If only one organ or system is involved, this is referred to as single-system LCH (SS-LCH) and has the best prognosis. If two or more organs or systems are involved, this is referred to as multisystem LCH (MS-LCH). MS-LCH is then stratified into low risk, high risk and very high risk, depending on whether any 'risk organs' are affected at diagnosis (haematopoietic system, liver and/or spleen) and by initial response to standard treatment regimes.

Epidemiology[2, 3]

- LCH is a rare disease that is more commonly seen in children but is increasingly recognised in adults.
- It affects 4-8 children per million each year:
  - Two thirds of children will have SS-LCH.
  - Children <2 years of age with MS-LCH, commonly have involvement of 'risk organs' and the highest mortality.
- It affects 1-2 adults per million each year:
  - In adults the mean age at diagnosis is 35 years, with 10% >55 years of age.
  - 69% have MS-LCH, 62% affecting the lung and 51% the skin.
  - 31% have SS-LCH, 51% involving the lung (most of whom are smokers), 38% bone and 14% skin.

Aetiology[3]

- Progress in the development of treatments for LCH has been hampered by its rarity but also by the question of whether it is a reactive or a neoplastic disorder.
- Current understanding suggests that LCH arises from a genetic mutation (BRAF V600E) occurring in a myeloid progenitor cell. It is thought that the developmental stage at which the mutation occurs determines the clinical manifestation of the LCH, although this concept is not proven.
- The mortality and permanent organ damage sometimes seen in LCH are most probably due to the harmful effects of an uncontrolled inflammatory response rather than unchecked proliferation of clonal Langerhans’ cells[1].

Presentation[3]

The presentation is variable and depends on the organ or system affected; it ranges from a self-healing disease to chronic recurrences[4].

The spectrum of symptomatic disease varies from a single bony lesion to multiple bony, skin and visceral lesions.

Clinical features of LCH (listed by organ system)[3]

Bony lesions - osseous LCH

- Bone is commonly affected (75% of cases).
- Well-localised bone pain is a common presenting symptom, with pain during both activity and rest.
- Lesions are lytic.
- Bone pain usually correlates with a radiologically evident lesion but lesions can be painless.
- There may be tender swelling of the soft tissue overlying the bone.
- Common sites for bone LCH are skull, proximal femur and ribs.
- Multifocal bony LCH is predominantly diagnosed in pre-school children.
- Rarely, bone lesions may cause pathological fractures.

Skin and mucous membranes

- Skin involvement occurs in 34% of patients.
- Rashes may be macular, papular, nodular or petechial.
- Skin rashes in neonates may regress spontaneously.
Scalp lesions may be scaly.
Any mucosal tissue can be affected; ulceration and bleeding can occur.
Oral LCH may give rise to recurrent gingival ulceration and 'floating teeth'.
When the skin of the inner ear is affected, this may cause copious otorrhoea.
Purpuric lesions to the nailbed occur with nail involvement.

CNS

CNS lesions are most frequently found in the hypothalamic-pituitary region where they lead to endocrine disorders involving the hypothalamic-pituitary axis:
- Diabetes insipidus (DI) is reported in 10-50% of patients.
- 53% of patients with DI develop growth hormone deficiency over 10 years.

LCH lesions at other sites in the brain may cause neurological symptoms as a result of mass effect.
- Orbit, mastoid and temporal bone lesions may lead to localised problems, including proptosis and sinusitis.
- Progressive neurodegenerative symptoms may arise decades after the initial presentation.

Lungs - pulmonary LCH

- Nonproductive cough, dyspnoea pleuritic pain or spontaneous pneumothorax.
- Abnormal CXR showing a reticular-micronodular pattern.
- Nodular/cystic pattern on a high-resolution CT scan.
- Isolated pulmonary LCH occurs frequently in adults, predominantly smokers (>90%), with a peak at 20-40 years of age. Women are slightly more likely to be affected than men.
- Pulmonary LCH is not considered high-risk but may proceed to multisystem involvement.

Lymphadenopathy

- This is fairly common.
- There are usually no symptoms unless the enlarged nodes damage or obstruct nearby organs and LCH cells are not typically identified in draining lymph nodes of affected tissue.

'Risk' organs - liver, spleen, bone marrow

- Diffuse infiltration or focal lesions of the spleen, liver or bone marrow are the most severe presentation and are defined as 'high-risk'.
- Most commonly seen in infants less than 2 years of age.
- Present with cytopenia or liver dysfunction.
**Gastrointestinal (GI)**

- GI lesions are rare.
- Sometimes associated with chronic diarrhoea, hypoalbuminaemia, weight loss or faltering growth.
- May lead to ulceration and GI bleeding.

**Other presentations**

LCH can involve other organs - for example, scrotal mass was a rare presentation in one study.

**Differential Diagnosis**

- Trauma.
- Seborrhoeic dermatitis.
- Candidal dermatitis.
- Eczema.
- Psoriasis.
- Intertrigo.
- Miliaria.
- Scabies.
- Varicella.
- Otitis externa.
- Other causes of oral ulceration.

**Assessment and investigations**[^3,4]

The diagnosis of LCH is based on histological and immunological examination of a lesional biopsy, which at the same time may provide a healing stimulus[^1]:

- Morphological identification of characteristic Langerhans’ cells.
- Positive staining for CD1a, CD207 (Langerin) and S100 cell markers is diagnostic.
- Birbeck’s granules on electron microscopy.

Investigations will otherwise depend on the clinical presentation but usually include[^5]:

- A thorough physical examination, including skin and oral mucosa, height and weight.
- Blood tests: FBC, clotting studies, U&E, LFT, urine osmolality.
- Plain X-ray - for bone pain or suspected bone lesions.
- Skeletal survey.
- CT/MRI scans of head and spine.
- Bone marrow biopsy may be required for staging.
- Endoscopy if GI involvement is suspected.
- For suspected pulmonary involvement, investigations are:
  - Plain CXR - may show upper lobe infiltrates.
  - Lung function tests - may show impaired diffusing capacity.
  - CT scan - may show typical changes of pulmonary LCH.
  - Bronchoalveolar lavage.
  - Bronchoscopy or surgical lung biopsy.

- Otolaryngological examination with audiogram may also be indicated.

**Management[^4,6]**

**General points**

- Treatment may be local or systemic, depending on the number and location of LCH lesions.
- Because LCH is rare, there are relatively few clinical trials and less experience available to inform treatment.
- Treatment may involve surgical excision, radiotherapy, chemotherapy, or combinations of these.
- The prognosis and treatment protocol depend on the number of organs involved, which organ systems are involved and the degree of organ dysfunction.
- Recommendations and protocols are available from the Histiocytosis Association[^7].

The following is an overview of current possible treatments, according to organs involved.

**Limited cutaneous disease**

- No treatment (it may remit).
- Topical steroids.
- Topical nitrogen mustard.
- Psoralen combined with ultraviolet A (PUVA) therapy.
Localised bone lesions

- Surgical curettage is the usual treatment (for accessible sites).
- Other treatments for bone lesions include:
  - Radiotherapy.
  - Intralesional steroids.
  - Bisphosphonates.
  - Early chemotherapy (vinblastine and prednisolone) for bony lesions at crucial anatomical sites.

CNS lesions

- Radiotherapy may be used for isolated cerebral tumours.
- Chemotherapy with cladribine or cytarabine is the most suitable treatment for pituitary/hypothalamic lesions, multifocal brain lesions or any brain lesion in multi-system disease.

Lymphadenopathy

- Surgical excision of single nodes with LCH.
- Regional node involvement may respond to a course of systemic steroids.
- Chemotherapy for nodes resistant to treatment.

Pulmonary LCH[8]

- Smoking cessation is essential. This may be the only treatment required.
- If smoking cessation fails and treatment is required, corticosteroids are the main treatment.
- Chemotherapy may be used for progressive disease not responding to steroids; however, this is a last resort because its efficacy is uncertain. Drugs which have been used in this context are vinblastine, methotrexate, cyclophosphamide, etoposide and, most recently, cladribine.
- Pleurodesis should be considered for recurrent pneumothorax.
- Lung transplantation can be considered for advanced disease.

Multi-system LCH

- The standard initial treatment in children is a combination of prednisolone and vinblastine with 6-mercaptopurine added after the first six weeks[9].
- Compared with children, adults experience increased neurotoxicity, worse myelosuppression and more steroid toxicity with the above regime. Cladribine or cytarabine are recommended initial therapy for adults requiring systemic therapy[2].
- Duration of treatment of twelve months compared with six months reduces the rate of reactivation[10].
Further reading & references

- Around 50% of patients with LCH do not respond to initial therapy or develop reactivation within five years \[2\]. Optimal treatment for these patients is, as yet, unknown:
  - A combined regimen of cladribine and cytarabine has shown some promise but is associated with high toxicity\[11\].
  - Vemurafenib, an inhibitor of the BRAF V600E mutation, has shown efficacy in preliminary studies \[2, 12\].
  - Stem cell transplantation may be used in patients with a poor prognosis whose LCH has not responded to conventional treatment.
- Patients receiving systemic therapy for LCH are at risk of Pneumocystis jiroveci infection and require prophylaxis.

Endocrinopathies

- DI should be treated with desmopressin.
- Hormononal deficiencies should be adequately replaced as soon as diagnosed.

Complications

Lifelong follow-up is required because of the possibility of late recurrence or late complications. Complications of LCH may occur at any time from presentation or many years later. Complications can arise even in patients without multi-organ involvement. It is estimated that about 50% of LCH patients have late complications of the disease or its treatment \[13\]. Complications include:

- DI (relatively common) - treated with desmopressin.
- Late relapse or progression to systemic involvement.
- Hypothalamic-pituitary dysfunction.
- Hearing loss.
- Cognitive dysfunction.
- Cerebellar dysfunction.
- Sclerosing cholangitis
- There may be an increased risk of other neoplasms \[8\].

Prognosis

- Prognosis depends on the extent and nature of organ involvement. The clinical course of LCH is extremely variable, ranging from a self-healing solitary bone lesion to widely disseminated life-threatening disease \[14\].
- Most cases have a good prognosis. In one study, five-year survival for low-risk patients was 99%, whereas the rate in patients with ‘risk organ’ involvement was 84% \[10\].
- For patients requiring chemotherapy, the response after six weeks of treatment is a major prognostic factor \[13\].
- Pulmonary LCH has a variable course. Most patients have a good prognosis: symptoms may be mild, and stabilisation or spontaneous improvement is possible. Some patients have progressive pulmonary LCH leading to progressive respiratory impairment \[8\].
- Neonates with LCH limited to the skin and mucous membranes have a good prognosis \[15\].