

# Leukaemia Section

## Review

## Langerhans cell histiocytosis

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### Abstract

Tumours derived from Langerhans cells (LCs) are divided into two main subgroups, according to the degree of cytological atypia and clinical aggressiveness: LC histiocytosis (LCH) and LC sarcoma. Both subgroups maintain the phenotypic profile and ultrastructural features of LCs. LCH is a clonal neoplastic proliferation of Langerhans-type cells that express CD1a, langerin, and S100 protein, showing Birbeck granules by ultrastructural examination. Here the clinicopathological of LCH will be discussed.

#### Keywords

Langerhans cell histiocytosis; CD1a; immunophenotype; Cytogenetics

### Identity

#### Other names

Langerhans cell granulomatosis, Solitary lesion: histiocytosis X, Eosinophilic granuloma; multiple lesions: Hand- Schüller- Christian disease. Cases with disseminated or visceral involvement: Letterer-Siwe disease

### Clinics and pathology

#### Disease

Tumours derived from Langerhans cells (LCs) are divided into two main subgroups, according to the degree of cytological atypia and clinical aggressiveness: LC histiocytosis (LCH) and LC sarcoma. Both subgroups maintain the phenotypic profile and ultrastructural features of LCs. LCH is a clonal neoplastic proliferation of Langerhans-type

cells that express CD1a, langerin, and S100 protein, showing Birbeck granules by ultrastructural examination (Swerdlow, et al ,2008. Swerdlow, et al, 2016).

#### Phenotype/cell stem origin

The neoplastic cells of LCH consistently expresses CD1a, langerin, and S100 protein (Chikwava, et al, 2004). In addition, the cells are positive for vimentin, CD68, and HLA-DR. CD45 expression and lysozyme content is low. B-cell and T-cell lineage markers (except for CD4), CD30, and follicular dendritic cell markers are negative. The Ki-67 proliferation index is highly variable (Pileri, et al ,2002). Expression of PDL1 is seen in many cases. The Langerhans cells are derived from mononuclear phagocytes macrophages and dendritic cells) or histiocytes. (Swerdlow, et al ,2008; Swerdlow, et al ,2016.)

#### Epidemiology

The annual incidence is about 5 cases per 1 million population, with most cases occurring in childhood. There is a male predilection, with a male-to- female ratio of 3.7:1. The disease is more common in white populations of northern European descent and rare in black populations. Primary LCH of the lung is almost always a disease of smokers, predominantly in young smokers, without gender predominance (Swerdlow, et al , 2008; Swerdlow, et al ,2016. Radzikowska, 2017).

#### Clinics

Patients with unifocal disease are usually older children or adults who most commonly present with a lytic bone lesion eroding the cortex. Solitary lesions at other sites present as mass lesions or

enlarged lymph nodes. Patients with unisystem multifocal disease are usually young children who present with multiple or sequential destructive bone lesions, often associated with adjacent soft tissue masses. Skull and mandibular involvement is common. Patients with multisystem involvement are infants who present with fever, cytopenias, skin and bone lesions, and hepatosplenomegaly. There is an association between LCH and T-lymphoblastic leukaemia, with the leukaemia-associated TCR gene rearrangement present in the LCH cells, which has been considered as a trans-differentiation phenomenon.

The disease can be localized to a single site, can occur in multiple sites within a single system (usually bone), or can be more disseminated and multisystem. The dominant sites of involvement in the solitary form are bone and adjacent soft tissue (skull, femur, vertebra, pelvic bones, and ribs) and, less commonly, lymph node, skin, and lung. Multifocal lesions are largely confined to bone and adjacent soft tissue. In multisystem disease, the skin, bone, liver, spleen, and bone marrow are the preferential sites of involvement (Swerdlow, et al ,2008; Swerdlow, et al ,2016).

### **Pathology**

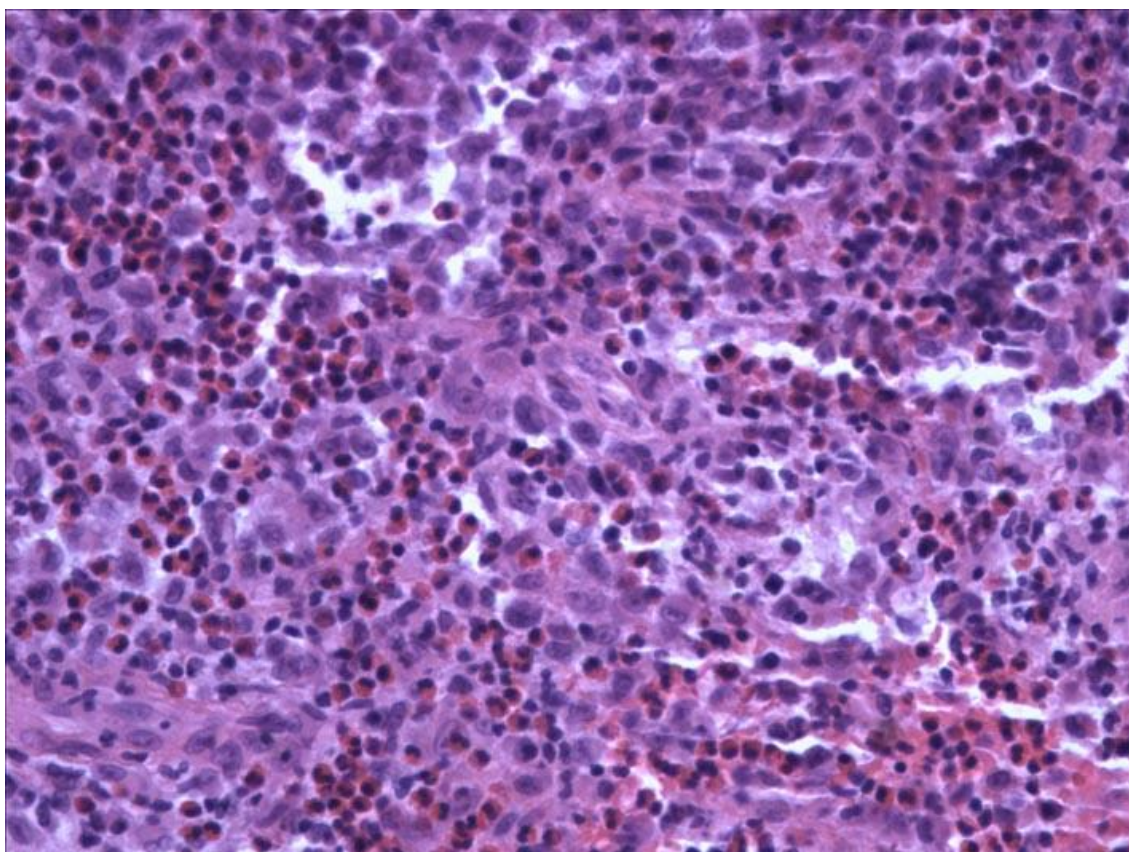
The LCH cells are oval, about 10-15  $\mu\text{m}$ , with grooved, folded, indented, or lobed nuclei and fine chromatin, inconspicuous nucleoli, thin nuclear membranes. Nuclear atypia is minimal, but mitotic activity is variable and can be high. The cytoplasm is moderately abundant and slightly eosinophilic. LCH cells are devoid of dendritic cell processes. The characteristic milieu includes a variable number of eosinophils, histiocytes (both multinucleated LCH forms and osteoclast-type cells, especially in bone), neutrophils, and small lymphocytes. Plasma cells are usually absent. Eosinophilic abscesses with central necrosis, rich in Charcot-Leyden crystals can be seen. In early lesions, LCH cells predominate, along with eosinophils and neutrophils. In late lesions, the LCH cells are decreased in number, with increased foamy macrophages and fibrosis. Involved lymph nodes have a sinus pattern with secondary infiltration of the paracortex.

Spleen shows nodular red pulp involvement. Large clusters or sheets of LCH cells accompanied by eosinophils can be found within other lesions (lymphomas and sarcomas). It remains to be determined whether these constitute a local reactive phenomenon or a trans-differentiation process. The ultrastructural hallmark is the cytoplasmic Birbeck granules, whose presence can be confirmed by langerin expression. The Birbeck granule has a tennis-racket shape, and is 200-400 nm long and 33 nm wide, with a zipper-like appearance.

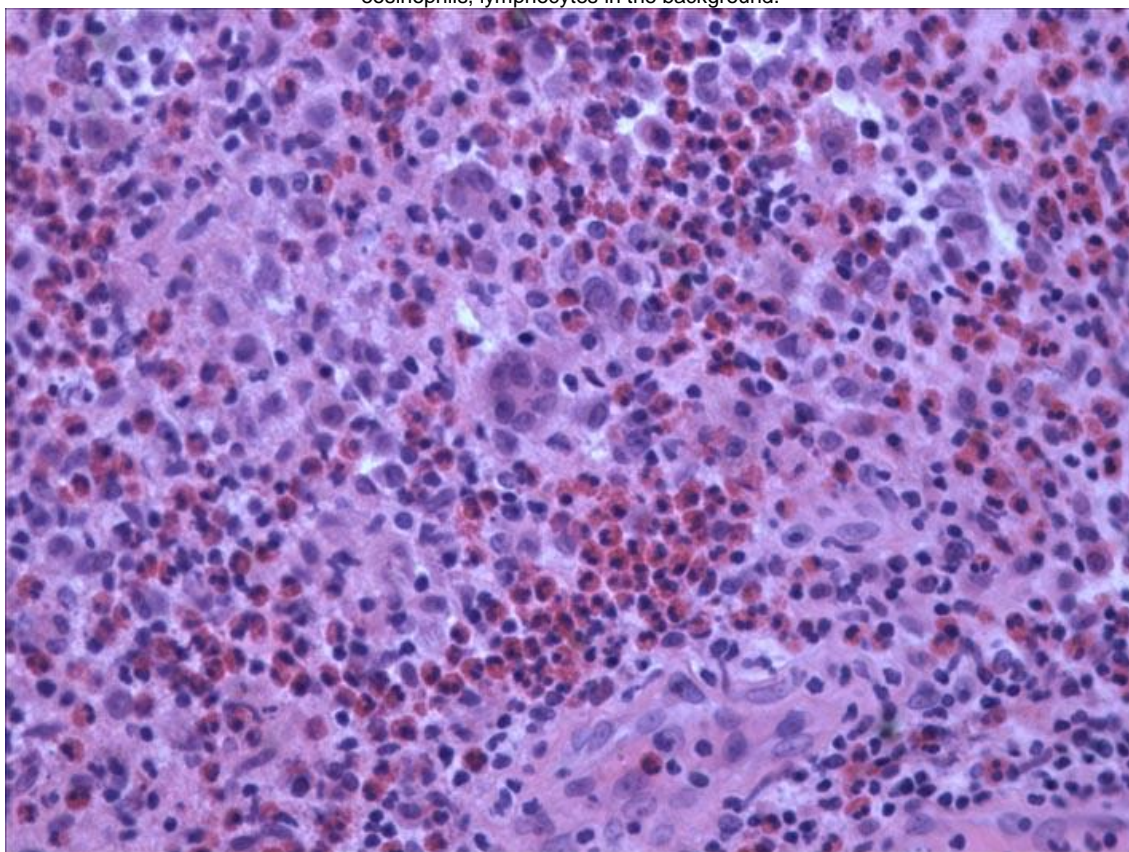


**Figure1.** Langerhans cell granulomatosis. Radiograph from a patient with a discrete punched-out bone lesion in upper femur.



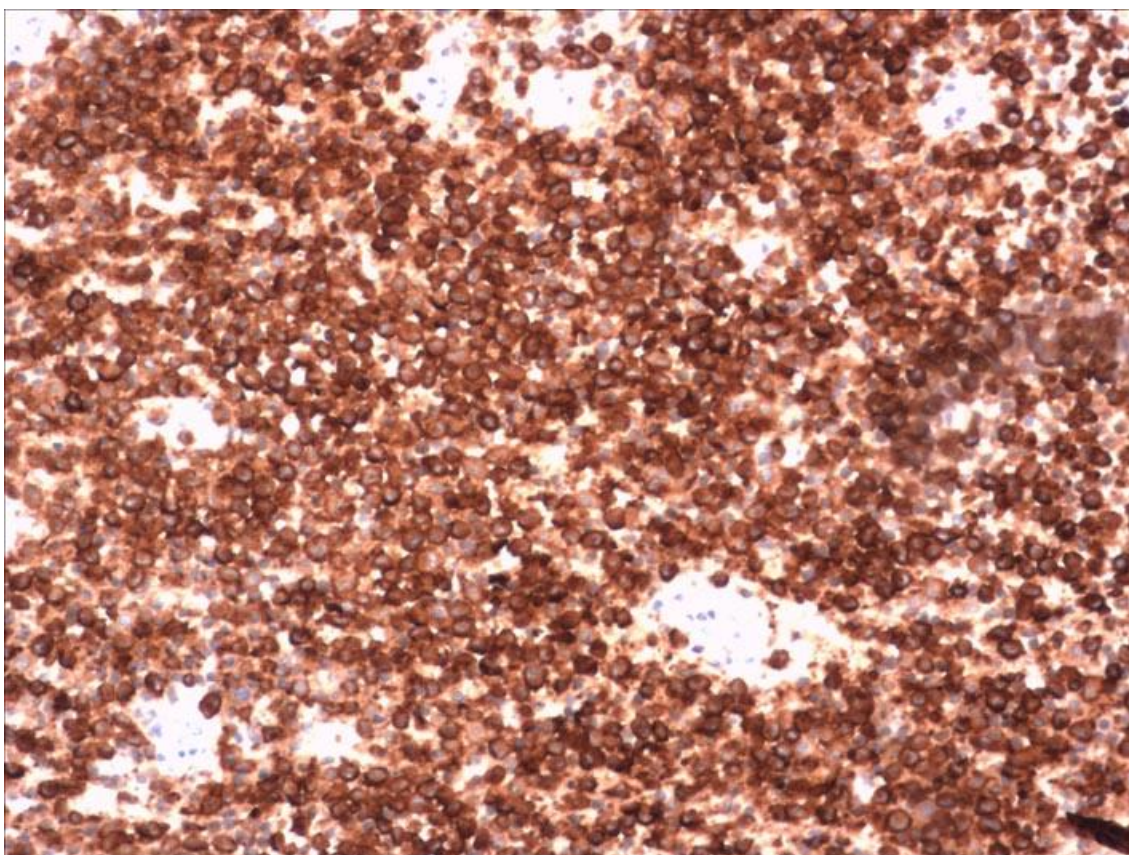


**Figure 2.** Langerhans cell granulomatosis. There are some Langerhans cells, with linear grooves in nuclei and scattered eosinophils, lymphocytes in the background.

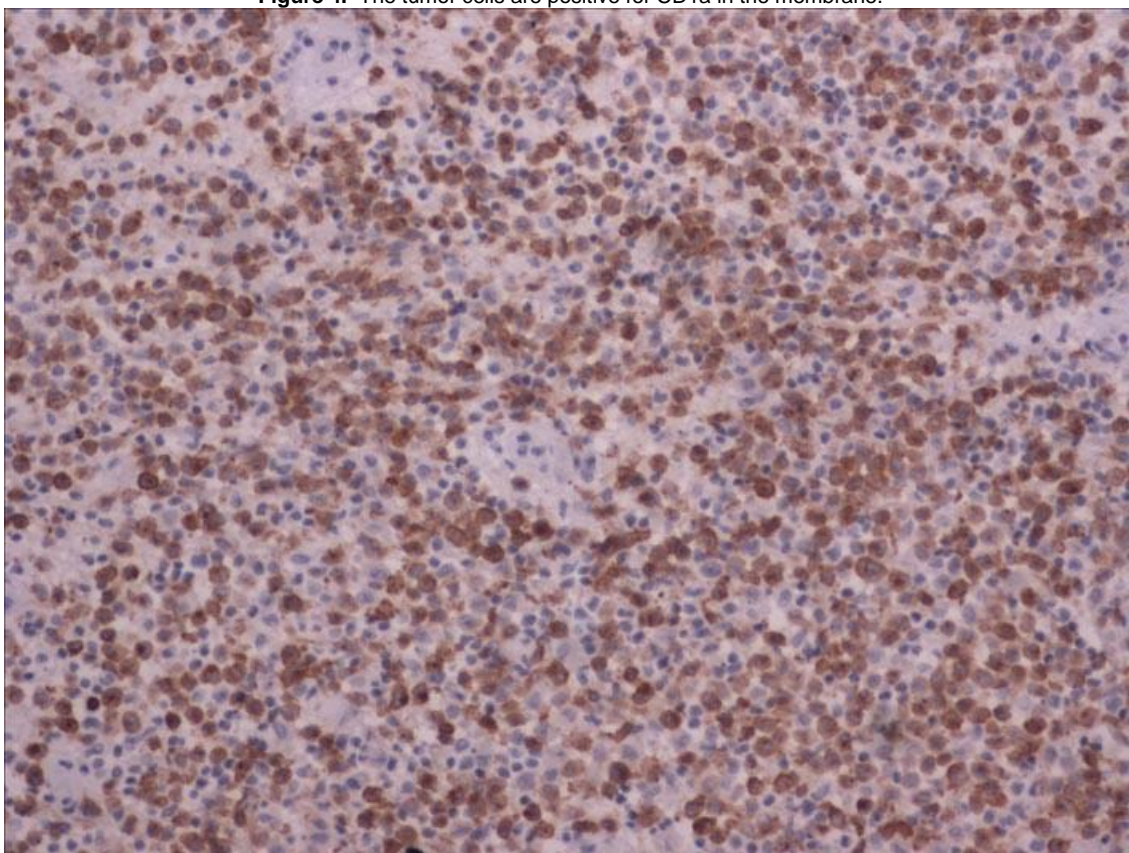


**Figure 3.** Langerhans cell granulomatosis. There are some Langerhans cells, with scattered eosinophils, lymphocytes in the background, and a multinucleated cell can be seen.



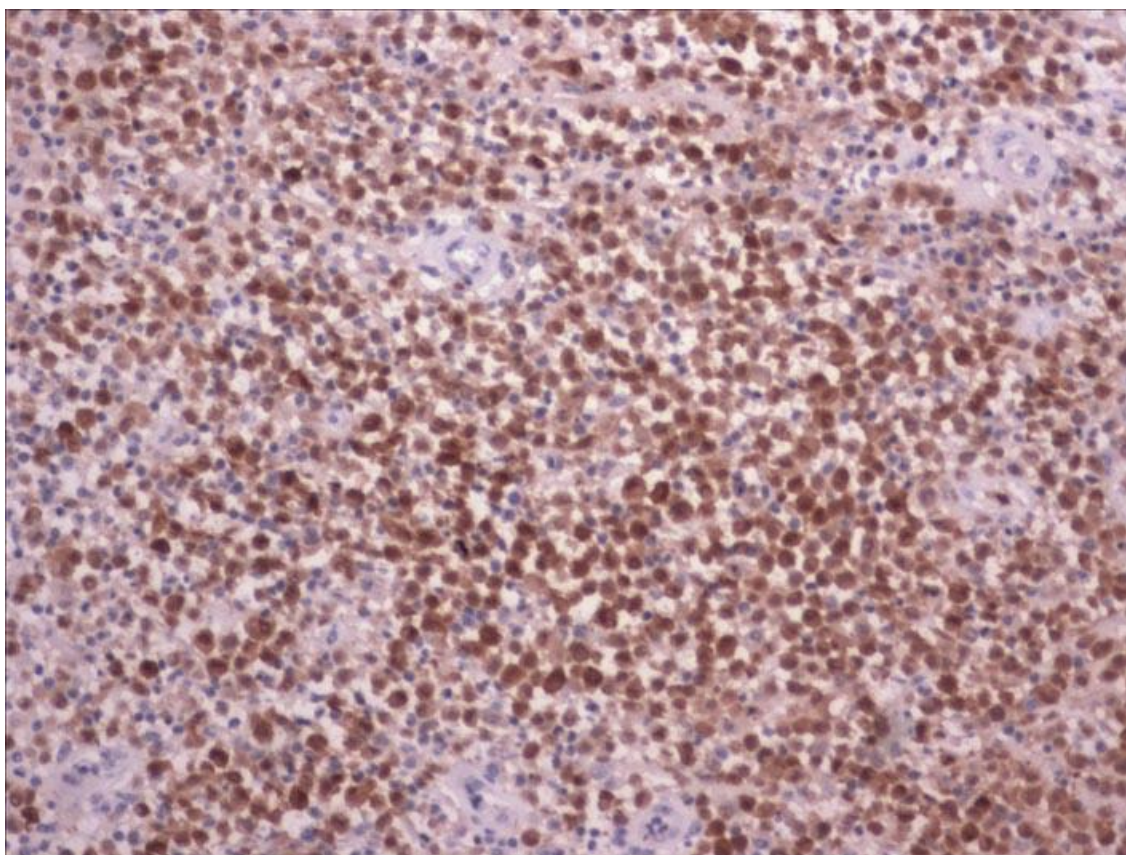


**Figure 4.** The tumor cells are positive for CD1a in the membrane.



**Figure 5.** The tumor cells are positive for langerin in the cytoplasm.





**Figure 6.** The tumor cells are positive for langerin in the nuclei and cytoplasm.

### **Treatment**

Treatment of LCH depends on the spread of the disease, affected organs, including lesions in critical organs and the degree of damage.

Systemic chemotherapy is recommended in the cases of multisystem LCH, with or without the involvement of critical organs, single system LCH with multiple lesions and single system LCH with lesions in specific sites.

There is no established standard of chemotherapy to date.

Although in children chemotherapy with vinblastine and prednisone proved to be effective, the results of treatment in adults turned out to be less successful. In patients with multiple bone lesions and affected lungs, significantly higher effectiveness of treatment with cytarabine or cladribine compared to vinblastine and prednisone has been shown. In some cases with solitary bone involvement, surgical removal of the focus is proposed or treatment of lesions with steroid injections. Patients with multiple bone lesions are treated systemically, surgically and/or with biphosphonates. Smoking cessation is the most important recommendation for Pulmonary LCH patients. Some authors recommend systemic steroid therapy in case of intensive symptoms from the respiratory system (Girschikofsky, 2013; Rigaud, 2016). The treatment of progressive

Pulmonary LCH is based on cladribine or cytarabine as salvage therapy (Radzikowska, 2017).

Basing on extrapolated observations made during randomised trials in children, various types of cytoreductive therapy (methotrexate, vinblastine, 6 mercaptopurine, etoposide) have been applied in adult LCH patients. However, the disease in adults runs a diverse clinical course and many drugs are differently tolerated. Vemurafenib and other BRAF inhibitors offer new possibilities for targeted LCH therapy in patients with relevant mutations. (Epaud, 2015; Héritier, 2016).

MAP kinase inhibitors (Sorafenib, trametinib and cobimetinib) have been reported to be effective in patients with aggressive form of histiocytosis. Furthermore, it is vital to remember that presented mutations in Langerhans' cells are not excluding mutations, thus, in particular cases, there are recommendations to apply double targeted therapy (Kolenova, 2017).

### **Prognosis**

The clinical course is related to staging of the disease at presentation, with  $\geq 99\%$  survival for unifocal disease and 66% mortality for young children with multisystem involvement who do not respond promptly to therapy. Involvement of the bone marrow, liver, or lung is considered a high-risk factor. Progression from initial focal disease to

multisystem involvement can occur, most commonly in infants. Patient age, per se, is a less important indicator than is extent of disease. BRAF V600E mutation does not seem to affect prognosis. Systemic and (rarely) multifocal disease can be complicated by haemophagocytic syndrome (Swerdlow, et al , 2008; Swerdlow, et al ,2016).

## Cytogenetics

LCH has been shown to be clonal by X-linked androgen receptor gene (HUMARA) assay, except in some adult pulmonary lesions. About 30% of cases have detectable clonal IGH, IGK, or TR rearrangements, including some cases with both T-cell and B-cell gene rearrangements. Approximately 50% of cases harbor BRAF V600E mutation. BRAF V600E mutation has also been identified in 28% of pulmonary cases, suggesting that at least many of these cases constitute a clonal proliferation. In addition, about 25% of cases are associated with somatic MAP2K1 mutations, almost always occurring in BRAF germline cases. Other BRAF germline cases may have somatic ARAF mutations (Swerdlow, et al ,2008; Swerdlow, et al ,2016). Mutations affecting other signaling pathway such as PIK3CA, PICK1, and PICK3R2 have also been described in LCH. (Emile, 2016)

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