22.3.9 Histiocytosis 5259 Chris Hatton

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of the cellular and molecular biology of dendritic cells, their precursors, and related cellular systems expands, the classification and nomencla- ture will change. A simplified classification of these diverse conditions is set out in Table 22.3.9.1. This chapter will focus on dendritic and macrophage disorders; malignant histiocyte/monocyte disorders are described in detail in Chapter 22.3.3 as acute myeloid leukaemia. Dendritic cell disorders Langerhans' cell histiocytosis Langerhans' cell histiocytosis (LCH) is now considered to be a dis- order derived from myeloid dendritic cells and not, as first thought, arising from Langerhans' cells of the skin. There remains some de- bate about the true neoplastic nature of LCH as clonality has not been demonstrated in all cases, though more recent gene expression profiling continues to lend weight to the concept that LCH is a clonal disorder. A high proportion of cases harbour cancer-associated proto-oncogene mutations and more than 50% of cases have the BRAF V600E mutation, often with additional mutations of the ERK pathway. It is likely that mutations occurring in early, less differen- tiated LCH cells will lead to widespread multisystem involvement, whereas mutations arising in more differentiated LCH cells are tissue restricted and lead to localized single system disease. Proliferations of these abnormal cells infiltrate various tissues—most commonly bone, skin, lymph nodes, spleen and liver, and the oral mucosa. The abnormal LCH cells express CD1a, S100, and CD207 (langerin), which are all of diagnostic significance. The cells also have charac- teristic Birbeck granules visible on electron microscopy. There is an additional group of disorders that mimic LCH which do not express these markers but express macrophage-associated antigens. The best-known example of this subgroup is Erdheim–Chester disease briefly described later in this chapter. Patterns of organ presentation were previously used to group these disorders into the eponymously named Hand–Schuller– Christian and Letterer–Siwe diseases—both describe multisystem involvement with LCH. The third entity was eosinophilic granu- loma, which described a localized lesion typically affecting bone. It is now accepted that this clinical classification is largely artificial and the terms are now redundant. Patients are better classified into those who present with a single system involvement and those with multisystem involvement. In young children, LCH commonly presents as a widespread ec- zematous rash not dissimilar to the rash found with candida infec- tion. In both adults and children, bone lesions are very common and typically lytic, and they may be accompanied by a soft tissue mass. Any bone may be affected though special attention should be Table 22.3.9.1 Histiocytic diseases in summary Category Disorders Dendritic cell disorders Langerhans' cell histiocytosis Follicular dendritic cell sarcoma Interdigitating dendritic cell sarcoma Juvenile xanthogranuloma Erdheim–Chester disease (non-LCH) Macrophage-related disorders Haemophagocytic Lymphohistiocytosis Rosai–Dorfman disease Malignant histiocyte disorders Monocytic acute myeloid leukaemia Histiocytic sarcoma

 paid to involvement of the skull or the jaw, as these sites confer risk of central nervous system involvement. The presence of diabetes insipidus should always be sought, as infiltration of the pituitary is a characteristic and common finding in LCH. While posterior pitu- itary involvement is well recognized, anterior pituitary failure may also occur necessitating a full endocrine assessment. A rare form of neurodegeneration affecting the dentate nucleus of the cerebellum or basal ganglia may occur, giving rise to profound ataxia and cog- nitive impairment. Liver, spleen, and lymph node involvement is also common in patients with multisystem disease. Liver and spleen involvement confer a poor prognosis. Bone marrow infiltration is likely to be common in patients with multisystem disease though this is not well characterized. An unusual but well-described presentation of LCH is a discharging ear with associated mastoid bone erosion. A seem- ingly distinctive entity—pulmonary LCH—causing lung

infiltration affects smokers. Cessation of smoking may lead to an improvement in this condition. The important consideration is that LCH lesions may be localized (single system) or multisystem in nature and their clinical manage- ment and treatment is based on this principle. In the modern era, the finding of LCH on biopsy should trigger a full staging protocol including a CT or positron emission tomog- raphy (PET)/CT scan, skeletal survey, bone marrow biopsy, endo- crine screen, and renal and liver profile (Table 22.3.9.2). Treatment The management and treatment of LCH depends upon staging. Patients who present with single system disease can be managed with simple curettage or local injection of steroids. Radiotherapy may be considered for adult patients presenting with single bone lesions. Patients presenting with multisystem disease will require sys- temic chemotherapy. In children, a number of clinical trials have attempted to improve on the standard induction regimen of vin- blastine and prednisolone (vinblastine 6 mg/m2 weekly for 6 weeks and prednisolone 40 mg/m2/day for 4 weeks and tailed). No def- inite benefit has been found for the addition of methotrexate or etoposide. Maintenance treatment with further courses of vin- blastine and prednisolone and 6-mercaptopurine has been found to prolong remissions. In adults there are no randomized trials though a number of chemotherapy agents have proved effective in inducing remission. The combination of vinblastine and prednisolone appears to be less effective in this older age group (20% attaining complete remission, CR), and low-dose continuous cytarabine (80% CR) or cladribine (60% CR) are therefore often the preferred regimens. LCH may be an aggressive disorder, so relapse is not uncommon. Patients who achieved durable remissions with their first-line induc- tion regimens may be retreated with the same agents. For patients who relapse early, a trial of one of the alternative drugs is reason- able. Some centres have consolidated such higher-risk patients with haematopoietic stem cell transplantation, with some success. Interestingly, BRAF mutation-positive cases have been reported to respond to vemurafenib—6 out of 18 patients who were known mu- tation positive benefited from the drug. The addition of a MEK in- hibitor may be beneficial. Non-Langerhans’ cell histiocytosis (Erdheim–Chester disease) The cells that give rise to this disorder appear to be macrophage derived. They do not stain with S100 proteins or group 1 CD1a glycoproteins, and electron microscopy of the cell cytoplasm does not disclose Birbeck granules. The pathology is characterized by xanthomatous or xanthogranulomatous infiltration with lipid-laden or foamy macrophages, usually surrounded by fibrosis. The pathog- nomonic Touton giant cells may also be seen. Bone biopsy may offer the greatest likelihood of reaching a diagnosis, and typically shows infiltration with foamy macrophages staining positive for CD68 but negative for CD1a. Approximately 50% of cases have the BRAF V600E mutation. The disease is very rare in children; the mean age of onset is 52 years. The most common presenting symptom is bone pain with characteristic symmetric infiltration of long bones causing osteosclerotic lesions. The disorder mimics classical LCH and is often multisystemic; patients are generally systemically unwell with fever and weight loss. Central nervous system involvement with diabetes insipidus occurs, though lymphadenopathy and splenic involvement are less usual than in classical LCH. Bilateral exoph- thalmos is a notable clinical feature. The management and treatment are as for LCH. A related disorder, at least pathologically, is juvenile xanthogranuloma which occurs in infants and children and affects the skin usually as a single nodule. This disorder is normally self- limiting and almost never multisystemic. Follicular dendritic cell sarcoma Follicular dendritic cell sarcoma (FDCS) is a rare malignant disorder derived from dendritic cells residing in the follicles of lymph nodes. The malignant cells are of mesenchymal origin and express markers of follicular dendritic cell differentiation including CD21, CD35, R4/23, and KiM4. The disorder may present at any age and typically, in the adult, manifests with painless lymphadenopathy often in the cervical region.

Multisystem involvement can occur, particularly in children, with patients experiencing marked B symptoms of sweats, fever, and weight loss. Management requires full staging with CT or PET/CT and for those patients with localized disease, meticulous surgical resection is indicated. Additional involved nodal irradiation may be con- sidered though a clear benefit of this combined approach remains unproven. Patients with multisystem disease are usually treated with lymphoma type protocols such as CHOP (cyclophosphamide, Table 22.3.9.2 Staging investigations for LCH Investigation Details Laboratory testing Full blood count, liver enzymes, urea and creatinine, TSH, LH, FSH, and glucose Biopsy Bone marrow biopsy if liver/spleen involvement, and/or cytopenias Imaging CT or PET/CT and MRI for CNS disease Other Water deprivation test Endoscopy (if malabsorption) CNS, central nervous system; CT, computed tomography; FSH, follicle stimulating hormone; LH, luteinizing hormone; MRI, magnetic resonance imaging; TSH, thyroid stimulating hormone.

 doxorubicin, vincristine, and prednisolone) or at relapse ifosfamide- and platinum-containing regimens such as ICE (ifosfamide, carboplatin, and etoposide). The prognosis relates more to the size of the presenting tumour and the mitotic rate than the clinical stage of the disease. Finally, there is an association with other disorders such as Castleman disease and low-grade lymphoma, the significance of which is yet to be determined. Interdigitating follicular cell sarcoma This is a very rare tumour with a clinical picture that closely resem- bles FDCS. Management is very similar to cases of FDCS although outcome is dependent on stage, with early-stage disease tending to have a good prognosis. Macrophage-related disorders Haemophagocytic lymphohistiocytosis Haemophagocytic lymphohistiocytosis (HLH) is a group of dis- orders characterized by activation of macrophages (macrophage activation syndrome) leading to a progressive and often fatal char- acteristic clinical presentation of pancytopenia, coagulopathy, de- ranged liver function, and fever. The disorder may be familial or acquired. Familial HLH In children and younger adults, the disorder is often caused by spe- cific genetic mutations, inherited in an autosomal recessive fashion, which result in disruption of cytotoxic T-lymphocyte and NK cell function. In this familial form of HLH, approximately 50% of cases are found to have mutations in the PRF1 or UNC13D genes. The PRF1 gene product perforin is one of the key molecules used by T cells and NK cells to kill virally infected cells. The UNC13D gene is implicated in the process of exocytosis—critical for the delivery of cytotoxic granules by T and NK cells. Other less common gene mutations have been described which may also be diagnostic for example in Hermansky-Pudlak and Griscelli syndromes affecting lysosome-related organelles (see Chapter 12.8). A failure to produce perforin or the production of an abnormal perforin protein, or a failure of delivery of cytotoxic granules causes marked derangement of both T-cell and NK cell function. Acquired HLH In adults, HLH is more commonly secondary to a number of trig- gering factors and predisposing diseases (Fig. 22.3.9.1) which include infectious agents such as HIV, Epstein–Barr virus, and cyto-megalovirus infection, autoimmune disorders, and haematological malignancy, most notably lymphoma. It is highly likely that acquired defects in the immune system underpin these disorders. Pathology of HLH Laboratory investigation reveals a marked and progressive pan- cytopenia. The bone marrow may be reactive and hypercellular in the early stages but becomes progressively more hypocellular as the disease advances. Careful inspection of the bone marrow as- pirate usually reveals macrophages that have ingested elements of the blood such as red cells, granulocytes, and platelets—so-called haemophagocytosis. While haemophagocytosis is characteristic of HLH it is by no means diagnostic, being found in a wide range of re- active states. In nearly all patients there is marked derangement of clotting with prolongation of the prothrombin

and activated partial thromboplastin time together with a marked hypofibrinogenaemia. Liver function is usually deranged though renal function is normally preserved at least in the early stages of the illness. Perhaps the most useful additional tests in clinical practice are the finding of a markedly raised ferritin (usually in the tens of thousands micrograms/ litre) and high plasma triglycerides. Clinical findings Patients with HLH are systemically unwell with marked pyrexia and weight loss. Patients may have lymphadenopathy and frequently have hepatosplenomegaly on clinical examination. There may be Bacteria Other Mycobacterium tuberculosis Rickettsia spp Escherichia coli Staphylococcus spp Toxoplasma spp Other HIV Other herpes Epstein-Barr virus Cytomegalovirus Vaccination or acute injuries Surgery Drugs Other Plasmodium spp Histoplasma spp Other Other Idiopathic Transplant Other AOD Other systemic autoimmune diseases Adult-onset still's disease Systemic lupus erythematosus Other neoplasms Other haematological malignancies Hodgkin lymphoma Haemophagocytic lymphohistiocytosis Leukaemia Lymphoma Other Leishmania spp Non-infectious triggers Viruses Triggering factors Parasites Fungi Predisposing diseases Fig. 22.3.9.1 Prompts and predisposing diseases to haemophagocytic lymphohistiocytosis. Reprinted from The Lancet, Vol. 383, Ramos-Casal M, Brito-Zerón P, López-Guillermo A, Khamashta MA, Bosch X, Adult haemophagocytic syndrome, Pages 1503–16. Copyright © 2014, with permission from Elsevier.

 clinical evidence of the associated coagulation derangement with purpura and bleeding. Central nervous system symptoms and signs reminiscent of encephalitis have been reported in a high proportion of cases. Investigations Laboratory investigations in a patient suspected of haemophagocytic syndrome include a full blood count, liver and renal function, lac- tate dehydrogenase, serum ferritin, lipid profile, coagulation screen, autoimmune serology, C-reactive protein, viral screen to include Epstein–Barr virus and cytomegalovirus polymerase chain re- action, bone marrow biopsy, and cerebrospinal fluid examination. Serology for possible infective causes should be considered. Lymphadenopathy should be biopsied as underlying lymphoma is a common cause. Mutation analysis looking for underlying HLH mu- tations (mentioned previously) should be performed. International collaborative groups led mainly by the Histiocyte Society have developed clinical criteria for the diagnosis of HLH (Box 22.3.9.1). Treatment HLH is a rapidly progressive and, without treatment, fatal condition. Modern protocols have successfully treated patients using a combin- ation of immune suppression and etoposide. A widely used protocol involves the use of ciclosporin, steroids, and etoposide and, in responding patients, consideration should be given to consolidating with stem cell transplantation. Allogeneic stem cell transplant is in- dicated for all patients identified to have a pathogenic gene defect. Patients with a macrophage activation syndrome secondary to auto- immune disorders such as Still's disease may respond to less aggres- sive therapy with prednisolone and ciclosporin alone. Rosai–Dorfman disease This is a rare disorder characterized clinically by massive cervical lymphadenopathy. A proportion of patients have paranasal sinus in- volvement which can lead to airway obstruction. Skin involvement may also occur. Pathologically, the disorder is characterized by the proliferation of macrophages within the sinuses of involved lymph nodes. A notable feature is the ingestion of lymphocytes by the proliferating macro- phages, known as emperipolesis. The disorder is thought to be re- active and not malignant, the lymph nodes slowly resolving over a few months. FURTHER READING Aricò M (2016). Langerhans cell histiocytosis in children: from the bench to bedside for an updated therapy. Br J Haematol, 173, 663–70. Brisse E, Matthys P, Wouters CH (2016). Understanding the spectrum of haemophagocytic lymphohistiocytosis: update on diagnostic challenges and therapeutic options. Br J Haematol, 174, 175–87. Brisse E, Wouters CH,

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of primary and secondary haemophagocytic lymphohistiocytosis: differences and similarities. Br J Haematol, 174, 203–17. Grom AA, Horne A, De Benedetti F (2016). Macrophage activation syndrome in the era of biologic therapy. Nat Rev Rheumatol, 12, 259–68. Henter JI, et al. (2007). HLH-2004: diagnostic and therapeutic guide- lines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer, 48, 124–31. Jordan MB, et al. (2011). How I treat hemophagocytic lympho histiocytosis. Blood, 118, 4041–52. Ramos-Casal M, et al. (2014). Adult haemophagocytic syndrome. Lancet, 383, 1503–16. Box 22.3.9.1 Diagnostic features for HLH Molecular features A Pathological mutations in PRF1, UNC13D, Munc18-2, Rab27a, STX11, SH2D1A, or BIRC4 or B Five of the eight following criteria are fulfilled: 1 Fever ≥38.5°C 2 Splenomegaly 3 Cytopenias (affecting at least two of three lineages in the peripheral blood):

Haemoglobin less than 100 g/litre

Platelets less than 100 × 109/litre

Neutrophils less than 1 × 109/litre 4 Hypertriglyceridaemia (fasting, >265 mg/dl) and/or hypofibrino genaemia (<1.5 g/litre) 5 Haemophagocytosis in bone marrow, spleen, lymph nodes, or liver 6 Low or absent NK cell activity 7 Ferritin greater than 500 mcg/litre 8 Elevated sCD25 (α-chain of soluble interleukin-2 (sIL-2) receptor) Adapted from Jordan MB, et al. (2011). How I treat hemophagocytic lymphohistiocytosis. Blood, 118, 4041–52 and Henter JI, et al. (2007). HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer, 48, 124–31.

Revision #1
Created 2026-01-22 16:42:32 UTC by Omar Ayman
Updated 2026-01-22 16:42:32 UTC by Omar Ayman