Paediatric histiocytic tumors

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Abstract

The histiocytoses are a diverse collection of uncommon diseases that include accumulations and proliferations of macrophages and dendritic cells. In this review we survey the majority of histiocytic proliferations that affect children. We emphasize the practical diagnostic features, differential diagnosis, and consider new information on Langerhans cell histiocytosis and related lesions. We describe the various non-Langerhans cell histiocytoses, especially the juvenile xanthogranuloma family of lesions including reticulohistiocytoma, Rosai–Dorfman disease, and overlap, combined and sequential histiocytic lesions.

Keywords ALK-positive histiocytosis; indeterminate cell histiocytosis; Langerhans cell histiocytosis; Langerhans cell sarcoma; reticulohistiocytoma; Rosai–Dorfman disease; xanthogranuloma, juvenile

Introduction

Histiocytes include the diverse family of monocytes/macrophages and the antigen processing dendritic cells (DCs). Concepts of their origin and development are still a work in progress; most notably, recent evidence from mice suggests that earliest macrophage migration is from the yolk sac to the liver and then the periphery under the influence of the ets family transcription factor PU.1. In humans, the early development from hematopoietic stem cell (HSCs) is better defined. HSC marrow precursors of myeloid cells, the common myeloid precursor, and the multilymphoid progenitor both contribute to the generation of macrophages and dendritic cells. The granulocyte-monocyte progenitor from the common myeloid progenitor gives rise to monocytes that not only produce both classically and alternatively activated macrophages, but also contribute to the dendritic cell population by providing inflammatory dendritic cells on demand. The macrophage-dendritic cell precursor has no granulocytic potential and gives rise to the common dendritic cell precursors that form classical dendritic cells, including Langerhans cells, and plasmacytoid DCs. These circulate as pre-classical DCs or pre-plasmacytoid DCs that mature when they enter the tissues. These are long-lived cells that regenerate locally with little replenishment from the marrow under normal circumstances. The macrophage-DC precursor also contributes to the macrophage pool by producing monocytes that exit the blood under inflammatory stimuli and give rise to tissue macrophages.

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Along their life-cycles histiocytes express a variety of markers that change as the cells mature and undergo functional activation. Only a few histiocyte-related antibodies are informative about the class of cells so immunohistochemical stains are best used in panels. Table 1 shows antibodies that react almost exclusively with macrophages, antibodies that are more exclusive to DCs, and those that are common to both.

Histiocytic disorders in general include reactive proliferations and neoplastic tumors. The reactive disorders span the gamut from innocuous lesions like dermatopathic lymphadenopathy, through the more serious secondary macrophage activation syndromes (activated by infections or malignancy), to the life-threatening various forms of primary (familial) hemophagocytic lymphohistiocytosis. On the other hand, the histiocytic tumors include disorders of dendritic cells lineage, disorders of the monocyte/macrophage lineage, and conditions that straddle the dendritic/monocyte-macrophage cell phenotype. The predominantly dendritic cell tumors include Langerhans cell histiocytosis and Langerhans cell sarcoma, while the primarily monocyte-macrophage type lesions include juvenile xanthogranuloma. These tumors have been shown to be clonal or to have recurrent genetic mutations supporting the proposition that they are bona fide neoplasms.

The Histiocyte Society and the World Health Organization (WHO) have proposed classification systems for histiocytic disorders/neoplasms. These two classifications are summarized in Table 2. While more comprehensive, the Histiocyte Society classification system is outdated. Since its proposition new entities, including indeterminate cell histiocytosis and ALK-positive histiocytosis have been described and the nomenclature of leukemias has been updated. The WHO classification is not unified and tumors that commonly affect the hematopoietic system are described separately from those that commonly occur in the skin.

This review will concentrate on the histiocytic tumors, starting with Langerhans cell histiocytosis and related disorders followed by the non-Langerhans cell histiocytosis. For each entity, a brief overview of clinical and radiologic features is followed by a more detailed description of the histologic appearances, a discussion of the differential diagnosis, and a brief update of recent discoveries.

Langerhans cell histiocytosis

Langerhans cell histiocytosis (LCH) is a clonal proliferation of abnormal histiocytic cells. In addition to also having Birbeck granules, LCH cells have an immunohistochemical staining profile similar to Langerhans cells (LCs). Although these features may suggest that LCH arises from LCs, studies have showed that LCH cells exhibit a unique transcription profile that separates them not only from plasmacytoid and myeloid dendritic cells, but also from epidermal LCs indicating a distinct dendritic cell origin from myeloid marrow precursors.[1]

The earliest descriptions of LCH date as far back as the 1890s. The now mostly retired early eponyms and historic names of LCH and their clinical correlates are listed in Table 3.

LCH primarily affects children (8–9 per million children per year) and is increasing in incidence in adults. Any organ system can be affected with the most frequently affected organs

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Antibodies and enzymes informative for histiocytes in tissues

Histiocyte	Stain
Macrophages	CD14, CD68, CD163, acid phosphatase, non-specific esterase
Langerhans cells	CD1a, Langerin, S100
Mature DC	CD83, DC-LAMP, hi-fascin, S100, HLA-DR
Dermal Interstitial Macrophage	F13a, CD163
Dermal Interstitial DC	S100, CD1a
Plasmacytoid DC	CD123, CD68
Follicular DC	CD21, CD23, CD35, clusterin, fascin

Table 1

being bones (80% of cases), skin (33%), and the pituitary gland (25%). The disease may be classified as either single system disease (SS-LCH) or multisystem disease (MS-LCH) depending on the number of organs involved. In SS-LCH only one organ or system such as skin or bone is involved. SS-LCH of bone can be either monostotic (a single lesion) or polyostotic (involving more than one bone). In MS-LCH two or more organs are involved, including liver, spleen, lung and bone marrow.

Up to half of LCH patients are asymptomatic and diagnosed on routine X-rays. Specific clinical manifestations depend on the site of involvement. Bone disease may present with pain, pathological fractures, vertebra plana, and/or local soft-tissue extension. Skin involvement often manifests as a persistent seborrheic dermatitis-like rash or papulo-nodular eruption involving flexures (axilla, diaper area etc) and/or the scalp. Newborns may also have papular lesions that regress spontaneously (known as cutaneous self healing reticulohistiocytosis or Hashimoto–Pritzker disease, but histologically indistinguishable from more systemic forms). Liver involvement may manifest with jaundice and direct hyperbilirubinemia and raised GGT levels due to LCH infiltration of the major bile ducts. The lungs are more commonly involved as part of MS-LCH. Pneumothorax, and respiratory compromise due to interstitial and peribronchial fibrosis are the results of pulmonary involvement. Irreversible diabetes insipidus and/or growth retardation are signs of active LCH affecting the hypothalamic-posterior pituitary axis. Late paraneoplastic-type of central nervous system (CNS) complications (often occurring many years later) commonly manifests as progressive ataxia, dysarthria, nystagmus, hyper-reflexia, dysdiadochokinesia, dysphagia and blurred vision (the result of bilateral focal cerebellar demyelination, not direct infiltration). Cytopenias may result from infiltration of the bone marrow but are likely to be cytokine mediated because the hematopoietic marrow is usually preserved. Gastrointestinal tract disease can result in diarrhea, protein-losing enteropathy, or malabsorption that is potentially life threatening. Non-specific B-type symptoms are common and can include fever, weight loss and fatigue. Because of these widespread and protean clinical possibilities, "staging" (a clinical and radiologic survey to map the extent of involvement) is indicated whenever LCH is first diagnosed at any site.

On X-rays, early and rapidly growing bone lesions may have a lytic appearance with poorly defined margins that mimic malignant disease whereas older and involuting lesions have an osteolytic center and sclerotic, sharply defined borders more characteristic of low-grade lesions such as chronic osteomyelitis. Pathologic fractures can confound the radiologic features. CT or MRI is helpful in determining the extent of bone lesions prior to biopsy, and PET scans can pinpoint activity. Pulmonary disease is best demonstrated by high-resolution CT scans that reveal subtle bronchocentric interstitial and cystic changes with sparing of the intervening lung. Late lung disease shows nodules, fibrosis, scarring and honeycomb changes. Pneumothoraces may occur as a complication of pleural bullae. Imaging of the liver may reveal the features of sclerosing cholangitis. Early CNS disease may show infiltration into the posterior pituitary stalk with loss of the MRI bright spot, or a space occupying choroid or meningeal mass. Late CNS disease, best seen on MRI, is characterized by symmetric foci of neuro-degeneration in the cerebellum and/or basal ganglia. Whole body FDG-PET scans are sensitive at finding new lesions and more informative of disease activity.

The gold standard for the diagnosis remains the histologic appearance and immunophenotypic confirmation. LCH cells are moderately large (15–25 μm) and oval, lacking the dendritic processes normally seen in dermal and inflammatory LCs. They are often nested/clustered or form sheets. The cytoplasm is often ample, pale eosinophilic while the nuclei are mostly single (sometimes binucleated) and grooved or complexly-folded (described as coffee bean- or envelope-shaped, respectively). Mitoses are variable and not atypical. Although variable numbers of interspersed eosinophils are noted in most lesions, their presence is not prerequisite in the diagnosis. Lesions rich in eosinophils may have eosinophilic abscesses with central necrosis and copious Charcot–Leyden crystals. Early lesions often contain sheets of LCH cells with many circumscribing T cells at the periphery. Osteoclast-type multinucleated cells and phagocytic macrophages can be present or even obscure the lesional cells in bone or lymph nodes, rarely in the skin. In regressing lesions the LCH cells dissipate and late biopsy of a healing lesion may be devoid of diagnostic LCH cells. LCH cells have a characteristic phenotype; S100, CD1a and Langerin-positive. They may have small, paranuclear foci of CD68 and HLA-DR staining. Cutaneous lesions are usually epidermotropic and favor the papillary dermis. Figure 1 shows a representative case of LCH involving the skin. Lymph node disease involves the sinuses spilling over into the paracortex to obscure landmarks. Focal loss of CD1a reactivity and high membrane HLA-DR expression suggestive of limited maturation may be seen in the infiltrated paracortex of lymph nodes but not in the requisite sinus involvement. Liver involvement is predominantly biliary with large caliber bile ducts showing intraepithelial LCH cells and a sclerosing cholangitis-like picture. In severe liver disease, biliary cirrhosis develops.[2] Early lung involvement is usually peribronchial with later spread into peribronchial alveolar walls leading to scarring fibrosis. Bone marrow involvement is frequently complicated by scarcity of LCH cells in small clusters and by reactive macrophage activation that can conceal the LCH cells. Splenic disease can also be challenging if no LCH nodules are

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