Advances in the understanding and management of histiocytic disorders 2015

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Abstract

Childhood histiocytoses encompass a range of illnesses that can present with a skin rash or single bony lesion that may spontaneously regress, or result in a systemic disease leading to multiorgan failure and death. For practical purposes they can be classified into four groups: Langerhans Cell Histiocytosis (LCH), Non-Langerhans Cell Histiocytoses (Non-LCH), Haemophagocytic Lymphohistiocytoses (HLH) and Histiocyte Lineage-related Malignancies. The establishment of diagnostic, staging and response criteria for LCH has enabled a series of international, randomised clinical trials that are the foundation of current evidence based treatment. Most cases respond to treatment but some children are left with significant permanent consequences affecting the skeleton and endocrine system. Cases of non-LCH are often difficult to diagnose and manage and require expert advice. Familial HLH is an inherited disease in which initial remission can be gained by chemotherapeutic or immunological strategies, but then requires allogeneic stem cell transplant for cure. There are a variety of leukaemias and sarcomas that are phenotypically derived from the histiocytic lineage. This article reviews the presenting features of histiocytic diseases and outlines current treatment regimes.

Keywords diagnosis; Haemophagocytic Lymphohistiocytoses (HLH); Histiocyte Lineage-related Malignancies; histiocytosis; Langerhans Cell Histiocytosis; non-Langerhans cell

Introduction

The term histiocyte was first used to describe a type of tissue macrophage, but in time has taken on a broader meaning which embraces a wide variety of cells of monocyte/macrophage lineage including dendritic and phagocytic cells. Dendritic cells are antigen presenting cells (APC) that ingest foreign material, process their antigens and present them to lymphocytes thereby initiating an immune response. Characteristic APC populations are found in many organs but were first described in skin by Paul Langerhans in 1868, who because of their dendritic processes, thought they were part of the nervous system. Whilst this did not prove to be the case, these epidermal APC were called Langerhans cells (LC). Other histiocytic cells have a primary role as tissue phagocytic cells (PC), cleaning up damaged or inflamed areas by ingesting and recycling foreign material and cellular debris. As with many rare diseases, the nomenclature for histiocytic disorders and their classification is complex and continually evolving as a result of increasingly sophisticated phenotypic, genotypic and functional analyses. An international effort to update the classification and nomenclature is currently underway. There are various sub-classifications relating to function and morphology. For the purposes of this article, Table 1 is based on the current clinical terms in common usage.

Whilst this article will focus on Langerhans Cell Histiocytosis, significant progress in the understanding and treatment of other histiocytoses will be discussed.

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Langerhans Cell Histiocytosis

Pathology and classification

In 1953, having identified similar abnormal histiocytic cells in eosinophilic granulomata, Letterer-Siwe and Schüller-Christian disease, Lichtenstein grouped them together under the single name of Histiocytosis X. Subsequently, it was found that these abnormal histiocytes closely resembled epidermal Langerhans cells (LC) and the name Langerhans Cell Histiocytosis (LCH) was adopted. Although pathological LCH cells do share many features in common with normal epidermal LC, recent experimental findings suggest that they may result from oncogenic mutations in precursor cells at different stages of differentiation. In 2010, Rollins' group reported finding mutations in the receptor tyrosine kinase RAS-BRAF-ERK signal transduction pathway in nearly 60% of a series of LCH cases tested. Very recently, the detection of BRAF mutations in cell free DNA in the plasma and urine of patients with systemic histiocytic diseases has been described. Based on further experimental findings looking at ERK pathway activation, it is proposed that mutations occurring early in macrophage-dendritic progenitor cells lead to widespread dissemination of affected cells, whereas mutation occurring in more mature cells at a later stage of differentiation results in localised disease.

Thus LCH appears not to be due to "reactive" epidermal LC responding to an inflammatory stimulus and migrating to and causing problems in other organs, but is caused by "oncogenic" transformation in precursors of related APC lineages. Does this mean LCH is cancer? The answer as so often with this disease is 'yes' and 'no'. There are such wide variations in the natural history of LCH, from unresponsive, rapidly progressive and fatal disease to cases of spontaneous remission that it is clearly not a malignancy in the same way as acute leukaemia. It is perhaps best regarded as a proliferative process that may have some malignant characteristics – an 'inflammatory myeloid neoplasia'.

LCH may involve skin, bone, lung, bone marrow, spleen, liver, bowel, lymph nodes, the pituitary gland and the central nervous system. Depending on organ involvement, staging distinguishes between single system (SS) and multisystem (MS) disease. MS disease involving bone marrow, spleen or liver is

Classification of histiocytic disorders

Langerhans Cell Histiocytosis

Non-Langerhans Cell Histiocytoses

- Juvenile Xanthogranuloma family
  - Cutaneous - Juvenile Xanthogranuloma
  - Cutaneous and systemic - Xanthoma disseminatum
  - Systemic - Erdheim Chester Disease
- Non-Juvenile Xanthogranuloma family
  - Cutaneous - Solitary reticulohistiocytoma
  - Cutaneous and systemic - Multicentric reticulohistiocytosis
  - Systemic - Rosai Dorfman Disease

Haemophagocytic Lymphohistiocytoses

- Familial
- Secondary (reactive)

Histiocyte Lineage-related Malignancies

- Leukaemias
  - Acute myelomonocytic and monocytic
  - Chronic myelomonocytic/juvenile myelomonocytic leukaemia
- Monocytic and histiocytic sarcomas

Table 1

associated with a worse prognosis and is designated risk organ positive (RO^+). Multisystem patients without involvement of these systems are designated risk organ negative (RO^-). In cases of SS, bony or nodal disease, several sites may be involved, which is then described as multifocal (MF) disease.

Epidemiology and aetiology

LCH is a rare disease. The British Paediatric Surveillance Unit study in conjunction with Newcastle University during 2003/5 revealed an incidence of 4 per million children (age 0–15 yrs) in UK & Ireland. More than half the patients presented with SS, single site, bony disease – or as previously classified, "isolated eosinophilic granuloma", whilst a quarter of the cases had MS disease (RO^+: RO^-, 1:3). During the period of the study three deaths were identified, all of which occurred in infants with MS RO^+ disease.

Twin studies and familial clustering suggest the possibility that a genetic predisposition may rarely exist in some cases. There is no convincing evidence to implicate specific environmental factors or infectious agents.

An association between malignancies and LCH has been described in many reports and a Malignancy Registry established by the Histiocyte Society in 1991 has identified over 150 cases worldwide – an association greater than would be expected by chance alone. In some cases the malignancy develops after treatment for LCH suggesting the possibility of therapy induced "second" malignancy. In others it is possible that LCH develops as a paraneoplastic phenomenon.

Presentation

Children present with a variety of symptoms and signs depending on which organ systems are involved as outlined in Table 2.

Skin

The rash often appears shortly after birth and if this is the only manifestation of LCH it is often diagnosed as eczema, allergic dermatitis or cradle cap. It is only when it becomes more florid or waxes and wanes for months despite "appropriate" treatment that referral to specialist services results in the correct diagnosis. The rash is very characteristic and if untreated excoriated and ulcerated lesions may develop in skin creases (Figure 1).

Bone

Single or multifocal osteolytic lesions can occur at any age, in any part of the skeleton and may present with pain or an obvious bony mass. Small lesions in long bones have a typical radiographic appearance as do multiple skull vault lesions that present as lumps on the head (Figure 2a). Base of skull and membranous bone lesions may have very dramatic imaging appearances that often lead to referral and investigation for suspected bone tumour. Importantly, mastoid disease may result in permanent hearing impairment, despite apparent "complete" resolution of the lesion. Jaw lesions typically present with "floating teeth". If extraction is avoided, these teeth may be saved by effective LCH treatment.

Lung

SS lung disease is rare in children. Lung involvement is often asymptomatic and found during screening for MS disease. Initially appearing as generalised reticulonodular shadowing, it may progress to widespread cysts, so-called honeycomb lung, with an inherent risk of pneumothorax. The lung was originally considered a risk organ in childhood LCH. However, it is now recognised that lung involvement does not confer a worse outcome and is no longer included in the group of risk organs.

Bone marrow and spleen

Peripheral cytopenia of one or more haematopoietic cell lineages may occur. Even in the presence of profound cytopenias the marrow may appear relatively normal suggesting that the effect is mediated by cytokine perturbation or peripheral consumption rather than marrow infiltration. LCH induced macrophage activation syndrome may contribute to this phenomenon.

There may be associated splenomegaly, but this is not invariably due to LCH infiltration as extramedullary haemopoiesis can also cause splenomegaly. Nevertheless, splenic enlargement or cytopenias reflect a poorer prognosis.

Liver

Whilst the liver is considered a risk organ, different patterns of hepatic dysfunction may be present. LCH cells may invade and damage larger bile drainage ducts causing cholestasis, eventually resulting in sclerosing cholangitis. Children with this type of damage are generally older and have less widespread, less aggressive LCH. Although they are likely to be long-term survivors they are at a high risk of developing cirrhosis. Alternatively, as part of MS LCH, children may present with hepatomegaly and some impairment of liver synthetic function with or without evidence of obstruction to bile drainage. These children tend to be younger and have widespread multisystem involvement with a relatively poor survival rate. This inflammatory process is probably driven by the inappropriate release