Non-Langerhans cell histiocytoses of the skin

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ABSTRACT

Histiocytic proliferations may be reactive or neoplastic. The neoplastic proliferations (histiocytoses) are subdivided into a few categories. One of these categories is the non-Langerhan's cell histiocytoses (NLCH). Cutaneous NLCH is a heterogeneous collection of conditions which can be sub grouped on the basis of the morphological appearance of the lesional histiocyte into xanthomatized, oncocytic, vacuolated, spindle-cell and polymorphous subtypes. The clinical characteristics and histological appearances of a variety of conditions within each subtype are discussed.

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Histiocytic proliferations may be reactive or neoplastic. The neoplastic proliferations (histiocytoses) are subdivided into a few categories. One of these categories is the non-Langerhan's cell histiocytoses, and it is this group of conditions which will be the main subject of discussion during this review with specific emphasis on skin involvement. Prior to that, a brief description of the fundamental characteristics and classification of histiocytes is presented.

General features of histiocytes. All categories of histiocytes are derived from the bone marrow by proliferation from a stem cell, and the derived cells migrate from the bone marrow to the blood as monocytes. Monocytes circulate through the body into various organs where they differentiate into histiocytes, which form part of the mononuclear phagocyte system.[1] The various categories of histiocytes (see later) share some common morphological and phenotypical features: 1. Their cytoplasm is eosinophilic and contains variable numbers of lysosomes 2. They bear the membrane receptor Fc for IgG and C3 component of complement 3. They express the common leuckocyte antigens CD45, CD14, CD33; class HLA I (A, B, C); class HLA II (DP, DQ, DR); and CD4 4. ATPasic and esterasic membrane enzymatic markers. Histiocytes are actively involved in the immune response by way of 2 distinct functions: 1. Phagocytic activity 2. Antigen presentation.

Broadly speaking, histiocytes can be divided into macrophages and dendritic cells. The former demonstrate a predominantly phagocytic role, while the latter are important in antigen presentation. The classification of histiocytes (and diseases involving each type) has been further refined,[2,3] such that the dendritic cells are subdivided into: Langerhan's cells (LC), dendrocytes and indeterminate cells.[2] Macrophages and dendritic cells (the 2 broad categories of histiocytes) are derived from a common marrow progenitor that has undergone divergent differentiation processes under the influence of environmental factors and various growth factors, such as interleukin-4 (IL-4) and tumor necrosis factor-alpha (TNF-alpha).[4] Macrophages are highly variable in morphology and size. Their cytoplasm contains numerous lysosomes in accordance with their main function of phagocytosis, and intracytoplasmic

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enzymes include lysozyme and esterase. Macrophages stain positively with certain monoclonal antibodies, most notably CD68, Mac 387 and LeuM1 (CD15). Polyclonal antibodies for lysozyme and alpha 1 antitrypsin are not specific and therefore, less helpful. Dendritic cells have an indented nucleus, and the cell outline demonstrates fine dendritic processes imparting a star-like appearance. They express factor XIIIa, CD1c and class II HLA antigens. Their main function is antigen presentation.[5] A subset of dendritic cells differentiates into Langerhan's cells (LC) after an indeterminate stage of differentiation. This maturation occurs in squamous epithelium, lymph nodes, spleen and bronchiolar epithelium. Langerhans cell express S100 protein and CD1a. Electron microscopy reveals tennis racquet-shaped inclusions within the cytoplasm known as Birbeck granules.

Histiocytic proliferations. These can be divided into: 1. Reactive histiocytic hyperplasias 2. Histiocytoses (histiocytic neoplasms). Reactive hyperplasias of histiocytes are more common than histiocytic neoplasms, and include granulomatous responses to certain infectious agents, foreign body reactions and reaction to degeneration of connective tissue. The histiocytoses are neoplastic proliferations of histiocytes, and may be benign or malignant.

In 1985, the Histiocyte Society proposed the following classification of histiocytoses: 1. Class I: Langerhan's cell histiocytoses (formerly histiocytosis X) 2. Class II: non-Langerhan's cell histiocytoses (non-X histiocytoses) 3. Class III: Malignant histiocytoses/ true histiocytic lymphoma.[6]

The rest of this review will concern itself with the class II histiocytoses (the non-Langerhan's cell histiocytoses) with specific reference to the skin. By definition this class of histiocytoses involve histiocytes which are not demonstrably of Langerhan's cell origin and therefore are negative for CD1a and lack Birbeck granules. They are however, positive for CD68 (macrophage) and factor Xiiia, or both.

On the basis of histo/cytological appearance, cutaneous non-Langerhan's cell histiocytoses are further subdivided into 5 groups of conditions depending on the relative abundance of xanthomatized, oncocytic, vacuolated, spindle or scalloped cells: 1. Predominantly xanthomatized type 2. Predominantly oncocytic type 3. Predominantly vacuolated type 4. Predominantly spindle-cell type 5. Polymorphous type.

Predominantly xanthomatized type. Xanthomatized cells with well-demarcated cytoplasm containing tiny vacuoles are the major cells in this group. Collections of xanthomatized cells are present in the dermis often admixed with multinucleate giant Touton cells. 1. Xanthoma and xanthelasma. These are associated with dyslipidemia. Xanthomas in general are divided into eruptive, tuberous, tendinous and plane subtypes. Each of these is further divided from the etiological point of view into genetic and secondary. 2. Papular xanthomas. Lesions consist of multiple muco-cutaneous papules that are yellow and non-confluent. Blood lipid levels are normal. Spontaneous regression of the lesions may occur.[7] 3. Xanthoma disseminatum (XD). A rare condition involving skin and mucous membranes in young men. Clinically the lesions are reddish papules, nodules or confluent plaques. They are bilateral and symmetrical, predominantly located on the face, the trunk and the flexures. Ocular mucosa and pituitary gland may also be infiltrated. Diabetes insipidus is present in 50% of cases and is usually mild and transitory, in contrast to that occurring in association with Langerhan's cell histiocytosis. Xanthoma disseminatum can also be associated with Waldenstrom's macroglobulinemia and there are some claims of an association between XD and multiple myeloma.[8]

Predominantly oncocytic type. Oncocytic cells with ground-glassy eosinophilic cytoplasm are the major component of this group.1. Multicentric reticulohistiocytosis. A rare condition predominantly affecting young females in which multiple erythematous skin nodules are associated with a destructive arthropathy. There is an association with hyperlipidemia, immune diseases and internal malignancy.[9,10] 2. Reticulohistiocytoma cutis (giant cell reticulohistiocytoma). This is the solitary variant of multicentric reticulohistiocytosis. Cutaneous infiltrates are rich in multinucleate oncocytic histiocytes with a large ground-glassy cytoplasm containing numerous PAS-positive inclusions.

Predominantly vacuolated type. Vacuolated cells with ill-defined clear cytoplasm are the major component of this group. 1. Benign cephalic histiocytosis. This occurs on the head and neck (almost always on the face) in children during the first year of life. It presents as a papular eruption in which the individual lesions are 2-3mm in diameter and red to yellow in color. The lesions usually regress after 2-5 years.[11] Histologically, it is a monomorphous vacuolated variant of xanthogranuloma (see later). 2. Generalized eruptive histiocytosis. This disease occurs in adults and presents with symmetrical red-brown papules. Mucosal lesions may be present. All the signs regress within a few years. This condition is regarded as a generalized variant of benign cephalic histiocytosis.

Predominantly spindle-cell type. Spindle-shaped cells are the main component of this group. 1. Spindle-cell variant of xanthogranuloma (see later) is a peculiar form of xanthogranuloma in children. 2. Nodular progressive histiocytosis. This presents as confluent papules and nodules on the face that progress to give a 'leonine' appearance, and do not spontaneously regress. Although mucosal lesions are rare[12] they have been reported for example in the larynx and mouth. In addition to the spindle-shaped histiocytes, the dermal infiltrate contains lymphocytes **(Figure 1)**. 3. Hereditary progressive mucinous histiocytosis **(Figure 2)**. This is a recently described entity which shows an

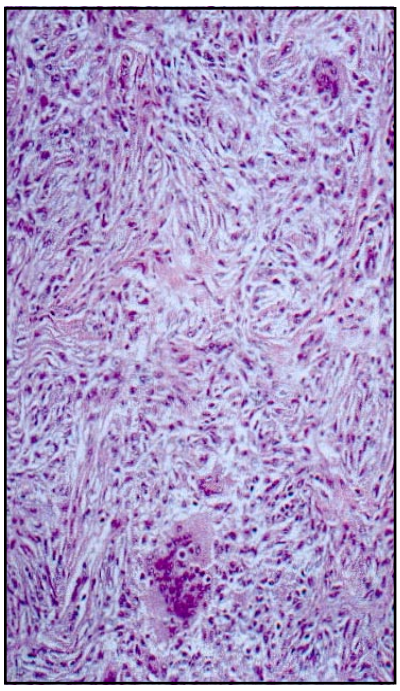

Figure 1 - Nodular progressive histiocytosis. Histiocytes are predominantly spindle-shaped and there is a focally storiform arrangement. Multnucleate giant cells are also present together with a sprinkling of lymphocytes.

autosomal dominant mode of inheritance. Patients have a progressive eruption of red-brown papules on the face and limbs. Nodular aggregates of epithelioid and tightly packed spindle cells are seen in the mid dermis. The cells are positive for factor XIIIa, and negative for S100 and CD1a.[13] 4. Familial sea-blue histiocytosis. A rare autosomal recessive disorder with skin involvement. It is characterized by disseminated infiltration of unusual macrophages containing granules which are blue-green on giemsa stain and rod-like cytoplasmic inclusions on electron microscopy.[14]

Polymorphous type. Juvenile and adult xanthogranuloma[15] (referred to in earlier sections) fit into this group. Both can be associated with ocular manifestations leading to glaucoma.[16] Adult xanthogranuloma may also involve the bone, in which case differentiation from Erdheim-Chester disease (see later) is a diagnostic problem. Histologically, this group is characterized by proliferations of histiocytes of variable morphology. The histiocytic component comprises 95% of the infiltrate in which mononuclear (predominant) and multinuclear forms are observed. Vacuolated, xanthomatized and spindle-shaped cells predominate in juvenile xanthogranuloma, whereas scalloped and oncocytic cells are the main feature of adult xanthogranuloma. Mixed infiltrates of small lymphocytes, plasma cells, neutrophils and eosinophils are also present.

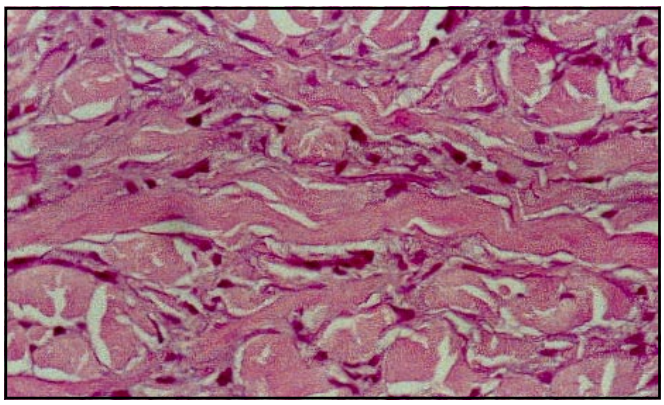

Figure 2 - Hereditary progressive mucinous histiocytosis. Epithelioid and spindle-shaped histiocytes are present together with mucin between collagen bundles. Sometimes, as in this case, the features may be subtle.

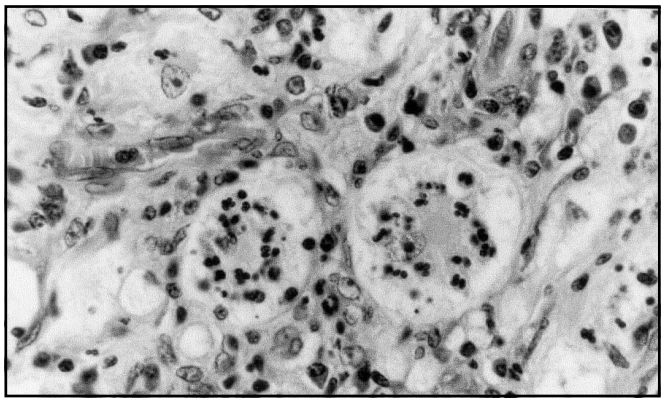

Figure 3 - Cutaneous Rosai-Dorfman disease. Large histiocytes having ingested smaller inflammatory cells (emperipolesis).

Other non-Langerhan's cell histiocytoses. There is a group of non-Langerhan's cell histiocytoses which deserve mention but do not fit snugly into the classification system outlined above. These are: 1. Rosai-Dorfman disease (Sinus histiocytosis with massive lymphadenopathy) 2. Erdheim-Chester disease 3. Indeterminate cell histiocytosis. Rosai-Dorfman disease (RD) is a rare disorder combining features of Langerhan's and non-Langerhan's cell histiocytoses. Lymph nodes are the most commonly affected site, followed by skin[17] such that over 10% of RD patients have cutaneous manifestations. There is a dense infiltrate in the dermis composed mainly of large histiocytes mixed with lymphocytes, plasma cells, neutrophils and erythrocytes (**Figure 3**). The histiocytes demonstrate emperipolesis (ingestion of the smaller accompanying cells) and are positive for S100. Positive CD1a staining has been observed in a few cases which suggests a relationship to Langerhan's cell histiocytosis and serves to blur the interface between class I and class II conditions.

Erdheim-Chester disease is a rare condition occurring in adults. Tissue infiltration by foamy histiocytes and symmetrical osteosclerosis of long bones are the main features. It can present as a systemic condition with life-threatening visceral involvement.[18] Cutaneous involvement may be in the form of xanthomas. As in the case of Rosai-Dorfman disease, there appears to be a relationship between Erdheim-Chester disease and Langerhan's cell histiocytosis: indeed, some reports have described patients with both conditions.[18] Indeterminate cell histiocytosis is a rare clinicopathological entity with features of both class I and class II histiocytoses, and thought most likely to be a variant of Langerhan's cell histiocytosis.[19]

The classification of histiocytes and their proliferations has been an altogether confusing and complicated issue in recent times. In relation to cutaneous histiocytoses the division into classes I-III is convenient and manageable with a cytological/ immunophenotypic/ultrastructural basis. In this brief overview it is hoped that the reader obtains a clear and relatively structured understanding of the variety of skin conditions that come under the rubric of non-Langerhan's cell histiocytoses.

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