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Editorial
Non-Langerhans cell histiocytoses

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Cutaneous histiocytic infiltrates can occur in a number of conditions e.g. infections (tuberculosis, leprosy, atypical mycobaterial infections, leishmaniasis, subcutaneous mycoses, etc.), trauma, foreign body reactions (silica, glass, etc.), metabolic (Gaucher's disease), and tumours (Hodgkin's disease, Lennert's lymphoma) etc. However, the term histiocytoses is reserved for the idiopathic cases. According to the Histiocyte Society,[1] this group is further divided into Langerhans cell (class I), non-Langerhans cell (class II) and malignant histiocytoses (class III) by their clinical features, histopathological characteristics and analysis of the predominant cells. The non-Langerhans cell histiocytoses (NLCH), also called non-histiocytoses X, are a heterogeneous group of frequently nonaggressive and self-healing entities which affect both children and adults. The clinical spectrum may range from banal cutaneous involvement as in dermatofibroma to severe systemic involvement as seen in hemophagocytic syndrome.[2] Histologically, these share the common denominator of proliferation of normal-looking histiocytes.[3] The individual cells may be spindle-shaped, scalloped, xanthomatized, vacuolated, or oncocytic. Variable mixture of these cells, along with Touton or foreign body giant cells, produce different histopathological patterns which may be monomorphous or polymorphous.

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Ultrastructurally, these cells always lack Birbeck (Langerhans) granules and are usually S-100 and CD1a negative.[3] Immunohistochemistry reveals an inconsistent pattern of reactivity to various antigens like S-100 protein; panmacrophage antigens EBM 1, Leu-M3; antigens functionally associated with phagocytosis (Fc receptor for IgG, complement receptor 3); markers of lysosomal activity (lysozyme 1-antichymotrypsin, alpha 1-antitrypsin; antigens associated with early inflammation (Mac-37, 27E10); antigens commonly found on monocytes but not tissue macrophages (OKM5, Leu-M1 [CD 15]); activation antigens (Ki-1 and receptors for transferin and interleukin 2); and others e.g. CD31, CD30, HM56.[4] Gene rearrangement studies reveal a polyclonal nature of infiltrate.[5]

The complex clinicopathological appearance and the usually benign course of disease are indicative of a reaction pattern rather than a neoplastic process. The cause of this remains unknown. Nonetheless, newer studies reveal the role of superantigens in immune mechanism stimulation after some focal injury e.g. insect bite, folliculitis,

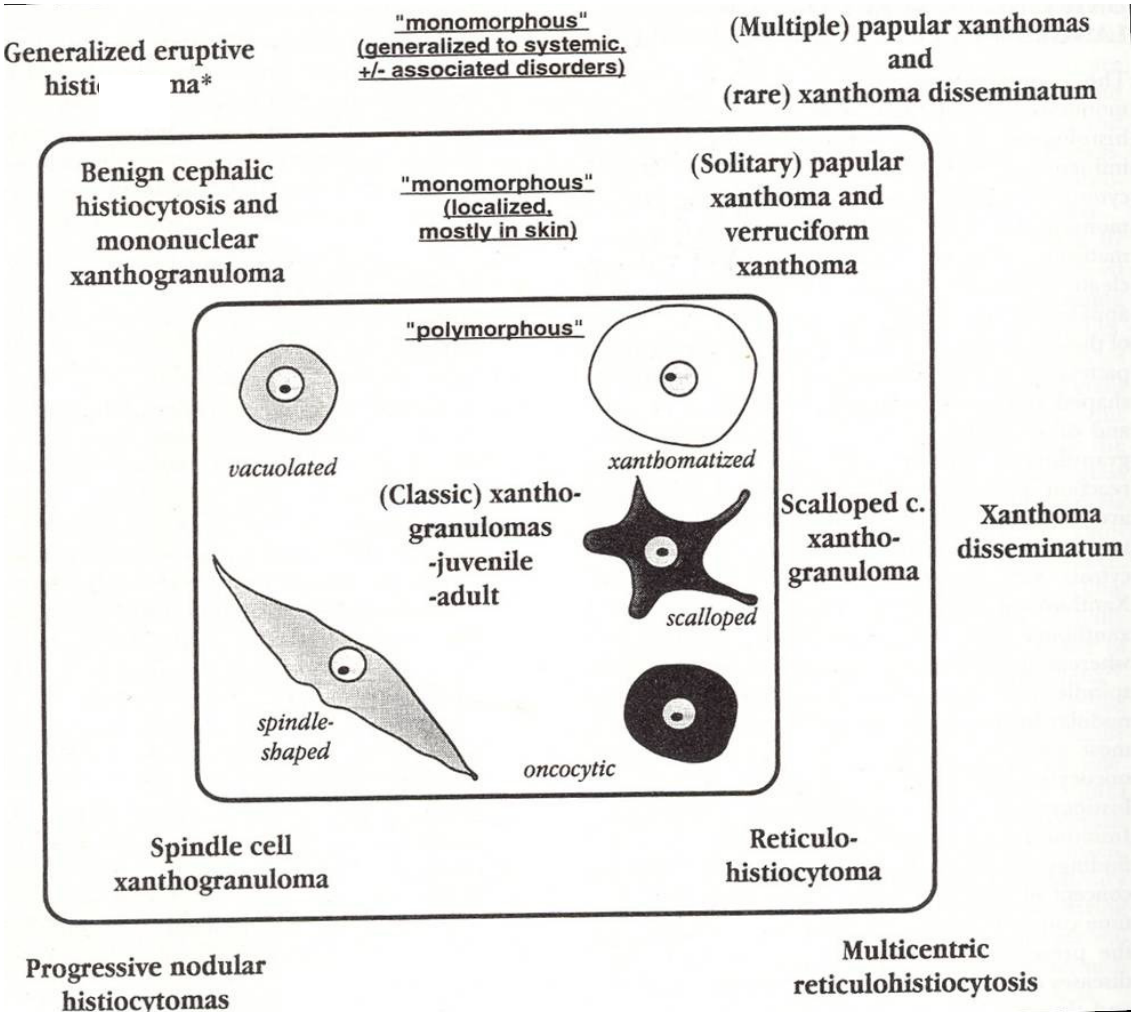

Figure 1 Unifying concept of non-Langerhans cell histiocytoses (NLH). Reaction pattern in different NLH entities [8].

trauma or a systemic insult. Inappropriate stimulation of macrophages, primary or secondary to some infective agents e.g. viruses (EBV, CMV, measles, etc.), bacteria (*Klebsiella, Brucella,* etc.), parasites etc; autoimmune or malignant process, leads to phagocytosis of blood cells. A possible pathogenic role of a defective function of *perforin*, a protein involved in the cytolytic processes and control of lymphocyte proliferation, has been speculated and mutations in perforin PRF1 gene have been identified in a subset of patients with hemophagocytic lymphohistiocytosis.[6] Inappropriate stimulation of macrophages in bone marrow and lymphoid organs leads to phagocytosis of blood cells and production of proinflammatory cytokines especially tumour necrosis factor-α (TNF-α).[7] TNF-α has been implicated as an important cytokine in the process and anti-TNF-α agents may prove an adjunctive therapy.[8,9]

Attempts have been made to unify the evolution of this diverse group. Under the influence of different sets of cytokines, the bone marrow-derived macrophage-monocyte cells develop into different cell lines (**Figure 1**).[8]

As far as treatment is concerned, apart from the excision of solitary lesions, it remains unsatisfactory for most of the conditions. Therapeutic studies are scanty due to the rare nature of these conditions and usually anecdotal reports are available.[7-10] Some of the conditions regress spontaneously, while others may improve as the underlying disease is treated. In secondary forms of disease treatment is generally symptomatic based on transfusion, correction of fluid and electrolyte disturbances and etiological therapies (antivirals, antibiotics, immunosuppressives or chemotherapeutic agents). Newer therapeutic options targeting specific mediators including TNF-α may emerge with better understanding of the pathogenesis.

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