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## The Langerhans cell histiocytosis: a disease in search of an identity

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Langerhans Cell Histiocytosis (LCH) is a proliferative disorder of activated Langerhans cells (LC) with highly variable biological behavior and clinical severity. It can affect many different organs, including the skeleton, skin, lymph nodes, liver, lungs, spleen, and the hematopoietic and central nervous systems. While the first descriptions were noted at the beginning of the 20th century, more than one hundred years later, the diagnosis and treatment of LCH remain have not been fully defined yet. In this issue of *Revista Brasileira de Hematologia e Hemoterapia*, Terra Babeto et al.<sup>(1)</sup> epitomize the ever-changing field in the understanding, definition and treatment of LCH. In their study, only one third (13 of 37) of the patients diagnosed with LCH had full confirmation, as defined by positive staining of CD1a or documentation of Birbeck granules at electron microscopy. However, when the unconfirmed cases were later reviewed, all patients with available samples were confirmed to have LCH. Thus, all patients were diagnosed and treated properly based on consistent clinical and histological features highlighting the seemingly consistent histology of LCH. In fact, the histopathology of the lesion is uniform regardless of the clinical severity of the disease and consists of collections of LC, interdigitating cells and macrophages, accompanied by T lymphocytes with variable numbers of multinucleated giant histiocytes and eosinophils. In this infiltrative process, the LCs are at the pathogenic top of this pyramid, where an intense networking 'dialogue' exists among all the involved cell types. Historically, Lichtenstein's unification of the three clinical forms of "Histiocytosis X" (eosinophilic granuloma, Hand-Schüller-Christian disease and Letterer-Siwe disease) was the culmination of several decades of observations that the proliferating cells in all of these disorders had the morphology of histiocytes. Although the origin of these cells was obscure this novel nosological category provided a new way of thinking about these unusual diseases. Later, electron microscopy revealed the presence of Birbeck granules in LCH histiocytes. These "racquet-shaped" cytoplasmic organelles are thought to be functionally important for antigen processing and presentation and appear to be uniquely present in LCs thus suggesting a shared lineage between these cells and the proliferating cells of LCH. Cell surface markers also support the pathogenic role of LCs in all forms of LCH. For example, histiocytes in LCH express CD207, also known as Langerin, which is also expressed on the surface of LCs and associates with Birbeck granules when it internalizes. However, Langerin can also be expressed by so-called Langerin-positive dendritic cells in the marginal zone of the spleen, indicating that it is not solely an LC marker. A more specific marker for LCs and pathologic histiocytes is CD1a, which as noted by Terra Babeto et al.<sup>(1)</sup> has become the gold standard for LCH diagnostics.

These conflicts in the definition of the disease probably reflect the suboptimal understanding of the pathogenesis of LCH. Because LCH has been demonstrated to be a monoclonal disease it may be considered a neoplastic disorder. However, different patterns of clinical involvement indicate other pathogenetic mechanisms. The occurrence of spontaneous remission and the benign histopathological appearance of the lesions in LCH suggest a reactive clonal disorder rather than a malignant process, at least in some cases. LCs, like other dendritic cells, have a critical role in the immune system and it has been suggested that LCH could be the result of immune dysregulation. Although no consistent immunologic abnormalities have been described, there is increasing evidence that LCH may be the result of an uncontrolled and abnormal proliferation of Langerhans cells secondary to either immune dysregulation or following exposure to a yet undetermined stimulus. In order to reconcile the clonal origin of the pathologic Langerhans cells with the evidence for immune dysregulation, a hypothesis has emerged that proposes that the monoclonal expansion seen in LCH could represent a host response to chronic antigenic stimulation. Under conditions of chronic stimulation, dominant clones of dendritic cells might emerge. These clones might still retain some ability to respond to normal immune regulatory loops, as exemplified by the therapeutic effect of cyclosporine.

The treatment of LCH over the years has reflected the changing concepts of the disease process. Indeed the difficulties in developing more effective therapies are linked to the deficiencies in the understanding of the pathogenesis of LCH. Since the 1970s we

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have known that although many organs can harbor proliferating LCs, only if organ function were disrupted was such involvement of prognostic significance. Patients could then be stratified into different risk categories based on the extent of their disease and the degree of organ dysfunction. This is the basis of the treatment of LCH, and the report by Terra Beбето et al.<sup>(1)</sup> exemplifies how these treatment paradigms can be used to effectively treat those unfortunate children. Treatment for patients with LCH is currently risk-adapted; patients with single-system disease confined to a single site usually require only local therapy or observation and patients with more extensive disease require systemic therapy. The best therapeutic option in these cases has not been defined and responses have been observed with short courses of steroids with or without the addition of chemotherapeutic agents. The treatment recommended by the Histiocyte Society for this group of patients includes a 6-week induction with prednisone and vinblastine, followed by continuation treatment with pulses of the same agents every 3 weeks for approximately 12 months. The prognosis for this group of patients is usually excellent although approximately 30% of the patients will experience disease reactivation that continue to respond to treatment. As noted earlier and in the report by Terra Babeto et al.,<sup>(1)</sup> involvement of the risk organs carries the worst prognosis. This high-risk group of patients is characterized by early age at presentation (usually < 2 years) and different degrees of liver, spleen or hematopoietic system involvement. Patients respond poorly to treatment, and the mortality rate is as high as 40%.

The advances in our understanding of the disease and the risk-stratification therapeutic approaches have slowly increased the cure rates; survival for children with LCH

exceeds 80%. However, patients with reactivation or chronic disease may experience severe permanent consequences that reduce their quality of life; these sequelae are characterized by fibrosis and degeneration that may affect the brain, lungs or liver. Thus, cure should not be our only goal; we must continue to unravel the intricacies underlying the pathogenesis of this disease and develop better treatments for those affected.

What was once known as Histiocytosis X continues to offer challenges to resolve, starting with its own identity. Decades of research have placed the disease in a context that floats between the paradigms of the reactive and the neoplastic disorders and somewhat limited our ability to approach the diagnosis and treatment of LCH in a more rational and effective manner. Recent advances have opened the field to a new and very provocative view of the disease. Molecular analyses of mouse models and human LCH samples suggest that the cell of origin in LCH lesions may not be the epidermal LC itself but a myeloid-derived precursor. Furthermore, advanced genomic technologies have revealed the presence of activating, somatic BRAF mutations in the majority of patient specimens. Together, these observations have produced a new picture of LCH as a myeloid neoplasm. These advances are likely to have profound implications for the use of targeted therapeutics in LCH. We may be back to the drawing board and back to Histiocytosis X?

## Reference

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