Blood spotlight on Langerhans cell histiocytosis

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Langerhans cell histiocytosis (LCH) is a rare disease mainly seen in children, but it can present at any age.1,2 The clinical manifestations range from a solitary, asymptomatic osteolytic lesion called “eosinophilic granuloma” that tends to heal spontaneously to multiple osteolytic lesions of the skull, intriguingly associated with exophthalmos and diabetes insipidus (DI), formerly called “Hand-Schüller-Christian” disease. In addition, in a small proportion of patients, especially toddlers, an ominous form of LCH (once described as “Abt-Letterer-Siwe” disease) may run an acute course with dissemination to various organs other than bones (particularly liver and spleen), thus shaping a multisystem disease as life-threatening as childhood acute lymphoblastic leukemia. Based on solid pathology findings and on a bit of intuition, Lichtenstein suggested in 1953 that these three conditions were part of a common disease spectrum, and he coined the term histiocytosis X, conveying the message that dysregulated proliferation of a histiocytic cell was at the heart of the problem but that the trigger for this was unknown.3

The diagnosis of LCH is based on finding in a biopsy, usually of skin or bone, a granuloma consisting of pale histiocytic cells with infolded nuclei, eosinophils, and multinucleated giant cells. Staining of the histiocytic cells for CD1a (and CD207 langerin) infolded nuclei, eosinophils, and multinucleated giant cells. Staining of the histiocytic cells for CD1a (and CD207 langerin) has become part of the diagnosis (the demonstration of Birbeck granules by electron microscopy is no longer required).1,3 The morphology of individual lesions is so uniform as to make it impossible for the pathologist to know whether a biopsy was from a patient with unifocal or multifocal disease, from a child or an adult, and whether the disease was clinically indolent or life-threatening; thus, after more than half a century, Lichtenstein’s notion is fully vindicated.

Systemic manifestations of LCH

Skin and bone lesions are the most frequent but fortunately the least threatening manifestations of LCH. At the other end of the spectrum, massive liver involvement and dysfunction may lead to rapidly fatal outcome or, sometimes, to late postinflammatory fibrosis (sclerosing cholangitis). In a minority of these patients, liver transplantation may prove curative, but in many, the disease reactivates in the transplanted organ.4 Pulmonary involvement is one of the most puzzling features of LCH. Children may have disseminated interstitial pulmonary nodules and cysts that are responsive to systemic therapy.5 Conversely, isolated pulmonary LCH is by far the most frequent manifestation in adults. A correlation with cigarette smoking has been clearly documented. Yet, in most cases, smoking cessation is not sufficient to stop the inflammatory process, and these young adults may show progression to multicystic metaplasia and become oxygen dependent. In such patients, the role of LCH-directed chemotherapy remains unclear, because existing reports are on small series, and no prospective studies have been conducted.6 End-stage organ failure often requires lung transplantation, and here too, disease recurrence may take place.

DI, resulting from destruction of the supraoptic-paraventricular nuclei in which vasopressin is produced,7 occurs in about 12% to 15% of patients with disseminated LCH. Osteolytic lesions of the skull base and facial bones predispose to DI, likely because of local vascular dissemination. Once DI is established, reversal may be exceptional.8 Thus, DI can be a disabling sequela, and it may progress to multiple anterior pituitary hormone deficiency.9 A small number of patients with LCH, especially among those with DI, may develop bilateral symmetric alterations in the cerebellar gray matter, in the basal ganglia, and in the brainstem. Histopathology from cerebellar biopsies and from autopsies revealed neuronal loss, axonal degeneration, and a profound T-cell inflammation. Its pathogenesis remains unsolved, but propagation from long-standing granulomatous lesions of the craniofacial bones to the intracranial space, with stimulation of chemokine/cytokine tissue damage or initiation of an autoimmune response to brain components have been suggested.10 Neurodegenerative LCH may be devastating and, unfortunately, no effective therapy is available so far.
**Treatment of LCH**

LCH tends to run a favorable course in the large majority of patients; indeed, most patients with solitary lesions do not need treatment as long as the lesion remains solitary (although it must be acknowledged that even biopsy itself may exert some therapeutic effect and may speed up the healing process). However, in a minority of cases, the disease may be aggressive and even life threatening. For a long time, the management of patients was conducted on an empirical basis, reflecting the different views and the uncertainty that have prevailed regarding the nature of the disease. Leukemia-oriented chemotherapy was used in children with disseminated disease by the Austrian-German group during the 1980s, with favorable response. Conversely, based on the concept of an inflammatory disease, anti-inflammatory agents, especially steroids, were used by the British group; although this achieved disease control in most cases, children with chronic and/or reactivating LCH developed unacceptable side effects from long-lasting steroid exposure. Since the early 1990s, an international cooperative group of pediatric hematologic-oncology specialists met the challenge of conducting 3 consecutive randomized trials in this orphan disease. Overall, these studies provided meaningful lessons: First, in LCH-I, which was a comparison of 6-month therapy with vinblastine or etoposide together with an initial 3-day pulse of prednisone, all patients with multisystem LCH (MS-LCH) were equivalent with respect to response, survival, disease reactivation, permanent consequences, and toxicity. However, early response and prevention of disease reactivation were inferior to results of the more aggressive (5-drug combination) and longer (12 months) DAL-HX 83 and DAL-HX 90 protocols, suggesting a need to intensify treatment. Second, in LCH-II, MS-LCH patients were stratified by risk (high risk being those with age <2 years and/or involvement of a risk organ such as liver, spleen, hematopoietic system, and lung) and were randomly assigned to the standard combination of prednisone and vinblastine vs additional etoposide. In both treatment arms, patients showed faster disease resolution and a higher survival rate than those in LCH-I, although the 44% reactivation rate was still higher. Lack of advantage, together with its reported leukemogenic potential, caused the discontinuation of study of etoposide in patients with MS-LCH. Third, in the LCH-III successor study, the efficacy of increasing intensity by adding methotrexate in risk-organ patients (treated for 12 months) and prolonging initial intense therapy if only a partial response was achieved by 6 weeks was tested but did not provide a better outcome; otherwise, extending the duration of treatment to 12 months proved superior to 6 months in reducing the rate of disease reactivation in children who had achieved disease control.

As a result of these trials, the former intuition, that patients with LCH should be stratified according to their very different risk of progression and treatment failure, has been validated. Patients with localized disease should be treated conservatively with very limited exceptions; patients with multisystem disease without involvement of vital organs should be treated with the combination of vinblastine and prednisone for a total duration of at least 12 months, which represents the standard of care in pediatric LCH, aimed at limiting the disease course and also permanent consequences. Yet there are still additional unmet clinical needs: about one third of patients who achieve complete control of the disease will suffer relapse during the following months, most often within the same tissue or organ(s) type(s) involved at presentation. Fortunately, whereas in childhood leukemia relapse is usually associated with very unfavorable prognosis, relapsed LCH is usually amenable to treatment with the same agents used before, or even with anti-inflammatory agents. For this reason, the term “reactivation,” which has been proposed since 1982, is now preferred to the term “relapse.” Beyond disease reactivation, a number of permanent consequences, including DI, neurodegeneration, sclerosing cholangitis, pulmonary failure, reduced linear growth and other endocrine dysfunctions, and bone deformities, represent quite a heavy burden for the quality of life of patients cured of LCH. But even more compelling is the remaining minority (20%) of MS-LCH patients with involvement of liver, spleen, bone marrow who fail to respond within 2 to 3 weeks, who still face an unacceptably high risk of early mortality in the range of 40%.

In these patients, very intensive chemotherapy, similar to that used for acute myeloid leukemia, turned out to be useful, whereas the role of hematopoietic stem cell transplantation remains uncertain. But this is definitely the subset of patients for whom novel experimental therapies derived from improved knowledge of LCH pathogenesis appear warranted.

**LCH: inflammatory or neoplastic?**

Although it has only localized manifestations in most cases, LCH must be considered a systemic disease. Unlike leukemia, LCH does not seem to arise from the bone marrow and to spread elsewhere. The basic lesion, the granuloma—the morphology of which has already been exhaustively described by nineteenth-century pathologists—is characteristically enriched in dendritic cells (DCs), reminiscent of the typical pattern of tissue reaction to an intracellular pathogen of which the tuberculous granuloma is the prototype. Again, it is since the nineteenth century that an infectious origin of LCH had been surmised but never proven, and extensive epidemiologic studies have failed to identify significant infectious associations. However, since the early 1990s, it has been claimed that clonal cell populations are present based on analysis through an X-linked marker (eg, the human androgen receptor assay; Humara) of lesional tissue from females with LCH. This finding is, per se, nonconclusive of cancer, because although cancer must be clonal, not every clonal population is cancer; indeed, clonal populations have been observed in benign disorders. Unexplained remission can occur in neoplasms, exceptionally even in widely metastatic cases; but spontaneous healing in LCH is not exceptional: on top of what is frequently seen in skin and bone lesion of children, the provocative observation that some young adult patients with pulmonary LCH remit after smoking cessation is one of the fascinating and incompletely understood features of LCH, suggesting that there may be many pathobiologic contributions to the disease process.

The fact that an animal model of LCH has been lacking for a long time has been a forceful stimulus to investigating pathogenesis by ex vivo studies and by looking for biomarkers. Clinical manifestations of LCH—aggressive chronic granuloma formation, bone resorption, and soft tissue lesions with occasional neurodegeneration—show similarities with those observed in other interleukin-17A (IL-17A)–related human diseases (Mycobacterium infection, Crohn’s disease, rheumatoid arthritis, and multiple sclerosis). In one study, peripheral blood samples from patients with LCH were put in culture; the resulting monocyte-derived DCs showed extended life span and propensity to undergo cell fusion, leading to the formation of multinucleated giant cells. These features make them excellent candidates to be at the origin of the characteristic granuloma. Remarkably, both of these properties—extended life span and propensity to fuse—were...
reproduced in culture by exposing normal control DCs to IL-17A; this phenomenon could be suppressed by exposure to anti-IL-17 antibodies and restored by re-exposure to IL-17A, suggesting an autocrine role for this cytokine with respect to granuloma formation. In the same study, patients with LCH were found to have high levels of IL-17A. However, a second group was unable to detect IL-17A messenger RNA (mRNA) or protein in samples from LCH patients. The authors suggested that the initial finding could be attributed to lack of specificity of the anti-IL-17A antibody. Subsequently, this laboratory failed to identify any cells in LCH lesions with IL-17A gene expression, concluding that evidence for IL-17A as a significant factor in LCH remained inadequate, thus beginning an IL-17 controversy in LCH. Yet the DC fusion activity of IL-17A in vitro was not dependent on an IL-17A antibody and has not been challenged, suggesting that IL-17A secreted by other cells might play a pathogenic role in LCH to foster tissue-aggressive giant myeloid inflammatory cell formation.

In spite of much recent progress on LCH that has just been reviewed, there remain three major questions to which we have only partial answers.

1. Why does a monocyte-derived DC become an LCH cell? The long-lasting question of a triggering pathogen in LCH has been revitalized by Murakami et al, who recently reported elevated amounts of Merkel cell polyomavirus DNA in the peripheral blood cells of 2 of 3 LCH patients with high-risk organ involvement, but not in the blood cells of 12 of 12 patients with low-risk LCH. Yet with lower viral loads, an elevated number of Merkel cell polyomavirus DNA sequences was detected in 12 LCH tissues compared with controls other than patients with dermatopathic lymphadenopathy. Previous studies of peripheral blood chromosomes showed that patients with LCH display an excess of spontaneous chromosomal breaks that are more evident during the acute phase of the disease; these findings resemble the genomic instability induced by respiratory syncytial virus (RSV), hepatitis C virus (HCV), or Epstein-Barr virus (EBV).

2. What are the key signals that drive monocyte-derived DCs to form a granuloma? Hutter et al showed that JAG2-mediated NOTCH activation confers phenotypic and functional aspects of LCH to DCs. Olsson et al found that monocyte-derived DCs treated with IL-17A express BCL2A1/BFL1, a prosurvival member of the Bcl-2 family. They also proposed that exposure to anti-IL-17A may decrease BFL1 and synergize with chemotherapy to eradicate LCH DCs. Identification of BRAF(V600E) mutation in 35 (57%) of 61 archived specimens of LCH tissue opened a novel research avenue in LCH. This finding was confirmed by a French
which has not yet been able to document $BRAF^{V_{600}E}$ in peripheral blood cells of patients with LCH, which would confirm that it is a somatic mutation within the lesional cells. In both studies, $BRAF^{V_{600}E}$ did not seem to correlate with age, clinical presentation, or outcome. Yet those data were not conclusive: (1) only about 40% of LCH patients have somatic mutations of $BRAF$, (2) retroviral transduction of $BRAF^{V_{600}E}$ in myeloid cells resulted in growth arrest and cell death, and (3) in genetically engineered mouse models, $BRAF^{V_{600}E}$ mutation in mature Langerhans cells was insufficient to develop LCH. In a very recent study of 100 LCH lesions, of which 64 carried the $BRAF^{V_{600}E}$ mutation within infiltrating CD207$^+$ DCs, patients with active, high-risk LCH were found to carry $BRAF^{V_{600}E}$ in circulating CD11c$^+$ and CD14$^+$ fractions and in bone marrow CD34$^+$ hematopoietic cell progenitors, but the mutation was restricted to lesional CD207$^+$ DCs in low-risk patients. In a new mouse model, the expression of conditional $BRAF^{V_{600}E}$ enforced under the langerin promoter was sufficient to drive LCH-like disease. In summary, although expression of $BRAF^{V_{600}E}$ in marrow DC progenitors was found to recapitulate the human high-risk LCH, $BRAF^{V_{600}E}$ expression in differentiated DCs resembled low-risk LCH. On the basis of these findings, we propose classification of LCH as a myeloid neoplasia.

3. Why do some people develop LCH? Studies of familial clustering of the disease have documented that about 1% of patients with LCH have another affected member in the family. When focusing on twin pairs, the rate of concordance is as high as 10% in nonidentical twins and an impressive 92% in identical twins. These data strongly point to a genetic component predisposing to LCH, even though efforts by Egeler et al to identify an LCH-associated locus through a genome-wide screening have not been successful. Interestingly, in this study, all patients had diploid genomes,
which, if anything, casts additional doubt on the neoplastic origin of LCH.

In conclusion, from the clinical point of view, LCH is a rare disorder with widely variable manifestations. After decades in which its pathogenesis remained elusive, recent findings suggest that somatic mutation occurring in a bone marrow myeloid progenitor drive a neoplastic process, although the same somatic mutation occurring at a more differentiated stage drives a self-limiting, inflammatory disorder. The finding of $BRAF^V_{600E}$ mutation in all concurrent pulmonary nodules suggests either multiple independent events or a true spread within the affected lungs. The monocye/DC plays a pivotal role and might have been genetically predisposed to becoming overstimulated by an infectious trigger.

Until now, improved outcomes for patients with LCH have accrued from empirically adopted chemotherapeutic regimens; recent exciting advances in the pathogenesis of LCH may suggest incorporating in a therapeutic trial prospective validation of the association of $BRAF^V_{600E}$ mutation with multisystem aggressive LCH and higher risk of treatment failure and exploring the use of vemurafenib in accurately defined subgroups of patients with LCH.

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Authorship

Contribution: M.A. designed and wrote the manuscript; and C.D. contributed to data interpretation, drew the figures, and contributed to writing the manuscript.

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