phase II study with a limited sample size (about 50 patients per arm) and follow-up (median, 2.6 years). The study reflected the real-life practice of allowing heterogeneous diagnostic criteria for ET and included several patients still treated with HC in the BAT arm. Further studies with a longer follow-up could provide additional data on the role of ruxolitinib in ET, with particular regard to the unmet clinical need of prevention of disease transformation. In this regard, a recently updated long-term, open-label study in 39 ET patients resistant or intolerant to HC did not register any case of transformation to post-ET MF or AML after a median exposure to ruxolitinib of 6.8 years.[7] The study demonstrated durable reduction in platelet and white blood cell counts and improvements in ET-related symptoms with ruxolitinib treatment.[7] Overall, the MAJIC-ET trial provides a relevant piece of information for a better understanding of the optimal treatment of patients with ET who are resistant or intolerant to HC. Current guidelines recommend interferon or anagrelide as second-line therapy for ET,[8] and these indications are confirmed by this study. At variance to patients with PV, ruxolitinib does not represent the first choice for most ET patients resistant or intolerant to HC, with the possible exception of those severely symptomatic, particularly for pruritus. Future studies of JAK2 inhibitors or other novel drugs in ET should further address the questions raised in this trial. Likewise, future randomized studies should include agents with different mechanisms of action reported in ET.[9,10] The key issue is the indolent nature of this disease and to carefully balance the possible benefits, risks, and costs of overtreatment.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

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DOI 10.1182/blood-2017-08-802165

Comment on Carrera Silva et al, page 1898

Finding active LCH cells in the blood

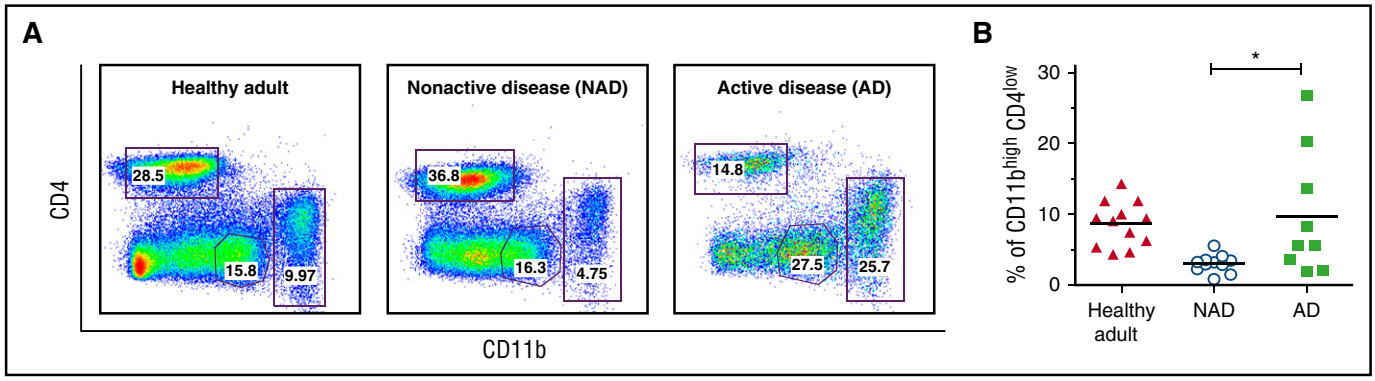
Oussama Abla THE HOSPITAL FOR SICK CHILDREN

In this issue of *Blood*, Carrera Silva et al demonstrate that $CD207^+CD1a^+$ circulating cells are increased in the peripheral blood of children with active Langerhans cell histiocytosis (LCH), in comparison with children with nonactive LCH and with healthy adults. Furthermore, $CD14^+$ monocytes express CD207 in these patients under the influence of thymic stromal lymphopoietin (TSLP) and transforming growth factor β (TGF-β).[1]

LCH is a rare disorder that can affect children and adults, characterized by the pathologic accumulation of immature Langerhans cells (LC) and inflammatory cells in organs such as bone, skin, liver, lungs, bone marrow, and brain. The clinical manifestations of LCH, particularly the pediatric form, are quite heterogeneous, with some patients having localized and self-limited disease and others developing fulminant leukemic-like forms. Although most patients with localized disease have a 100% cure rate, the outcome of those with multisystem, risk organ–positive disease is suboptimal, with a mortality rate of 15% despite the use of intensive chemotherapy.[2] A better understanding of the pathogenesis of LCH is, therefore, essential to improve the outcome of these high-risk patients.

Researchers have debated for more than a century whether LCH represents a reactive immune disorder or a result of malignant transformation of LC precursors.[3] We now understand that LCH is an inflammatory myeloid neoplasm with a high frequency of somatic mutations resulting in activation of the MAP kinase signaling pathway.[4] In 50% to 60% of LCH cases, *BRAF-V600E* mutations are present in their lesions. The next most common mutation after BRAF is *MAP2K1*, which encodes MEK1. In some cases, activation of the pathway is due to other BRAF (*BRAF-V600D*), *ARAF*, *NRAS*, *KRAS*, and *ERBB3* mutations.[4,5] BRAF mutations have been associated with risk organ involvement[6] and increased risk of recurrence.[7] In addition, detection of *BRAF-V600E* mutation in peripheral blood (PB) by polymerase chain reaction was 97% sensitive to active disease and represents a promising tool in assessing minimal residual disease (MRD) in high-risk patients.[7] However, larger studies are needed to validate these concepts; finding other markers of disease activity and the means to monitor treatment response is also warranted.

During inflammation, LCs are recruited in waves from the circulation. The first wave derives from monocytes and develops low CD207 (langerin) expression,[8] and the second wave derives from $CD1c^+$ dendritic cell precursors, which might lead to the long-term reconstitution of LCs.[9] Recent studies have shown that $CD1c^+$ cells develop LC-like phenotype in response to TSLP and TGF-β, suggesting a possible precursor role of blood



Increased CD11b fraction and circulating CD207$^+$CD1a$^+$ myeloid cells in peripheral blood of patients with active LCH as opposed to those with nonactive LCH and healthy adults. See Figure 1A-B in the article by Carrera Silva et al that begins on page 1898.

myeloid progenitors.[10] With inflammatory stimuli, CD207$^+$ cells and their precursors should theoretically circulate in the PB of patients with active disseminated LCH. In this study, Carrera Silva et al evaluated the presence of CD207$^+$CD1a$^+$ cells in the myeloid compartment of patients with LCH and assessed whether plasma levels of TSLP and TGF-β could drive the differentiation of CD207$^+$ LC-like cells.

The authors collected plasma from 22 LCH children with active disease (AD) and nonactive disease (NAD), who either were being observed or had received treatment. Peripheral blood mononuclear cells (PBMC) were collected from healthy adult volunteers. Myeloid and T-cell compartments were analyzed with appropriate flow cytometry methods, and TSLP and TGF-β plasma levels were measured by enzyme-linked immunosorbent assay. PBMC were stained with CD11b, CD2, and CD4 markers to compare the myeloid and T compartments of patients with AD and NAD LCH. The results showed a significant increase in cells expressing CD11b^{high} and CD11b$^{int/low}$ and circulating CD11b^{low}CD^{int} dendritic cells in patients with AD vs NAD LCH and healthy adults (see figure). In addition, there were circulating CD207$^+$ myeloid cells in the blood of patients with AD, as well as a higher percentage of circulating CD11b^{high} CD11c$^+$ CD207$^+$ monocytes and CD11c^{high} CD207$^+$CD1a$^+$ dendritic cells in patients with AD vs NAD. These data suggest that CD207$^+$CD1a$^+$ myeloid cells circulate in children with active LCH and could become predictive markers of active disease.

Furthermore, the study investigators found higher levels of TSLP and TGF-β in patients with AD, which correlated positively with the number of CD207$^+$ CD1a$^+$ monocytes, suggesting a role of these cytokines in the pathogenesis of LCH. In addition, plasma from patients with active LCH induced CD207$^+$CD1a$^+$ expression on sorted CD14$^+$ monocytes from healthy donors in vitro. Adding recombinant granulocyte-macrophage colony-stimulating factor, interleukin-4, and TGF-β on CD14$^+$ monocytes caused the highest expression of CD207 on day 4, which decreased by day 10. This is another indication that soluble factors in the plasma of patients with active LCH could be the driver of CD207 expression.

The current work is the first to suggest that we can now find active LCH cells in the peripheral blood. This opens the door to novel ways of MRD assessment from PB of patients with LCH. Monitoring treatment response and early signs of relapse by using PB could complement or substitute for conventional radiographic methods. These results, however, need to be validated in a larger cohort of children with LCH, particularly those with risk organ–positive disease, as well as in adult LCH. Additionally, these findings need to be correlated with *BRAF-V600E* and other MAPK pathway mutations in tissues and peripheral blood from patients with active LCH.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

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DOI 10.1182/blood-2017-09-805424