Erdheim-Chester Disease (ECD) is a non–Langerhans histiocytosis first described by Chester as “lipoid-granulomatose” in 1930. By 2010, only 350 additional cases had been added to the literature. Patients with ECD typically develop characteristic multifocal osteosclerotic lesions of long bones and may also develop extraskelatal histiocytic infiltrates of other sites including pituitary, orbit, retroperitoneum, kidneys, heart, lung, or central nervous system. Most patients with ECD die from their disease within 3 years of presentation.

Histocytic disorders have generally been divided into Langerhans cell histiocytosis (LCH) and non–Langerhans cell histiocytoses, with the assumption that LCH arises from pathologic epidermal Langerhans cells (LCs) and ECD and other non–Langerhans cell disorders arise from monocyte-macrophage lineage. ECD is defined by characteristic clinical presentation as well histology: Lesions are heterogeneous including inflammatory infiltrate along with foamy histiocytes with an immunophenotype distinct from LCH: CD68+, CD1a−, CD207−, S100−/low by immunohistochemistry, and Birbeck granules are absent (or rare) on electron microscopy. The figure demonstrates a representative hematoxylin/eosin-stained ECD lesion biopsy sample from a retroperitoneal, perinephric infiltrate (400× magnification). It shows the bland histiocytic infiltrate with foamy (xanthomatous) cytoplasm and interspersed inflammatory cells. Investigators have looked to the ECD lesions for clues to pathogenesis. Detailed immunohistochemical analysis of a small number of lesions found expression of many chemokines and chemokine receptors that direct lymphocyte and dendritic-cell activation and migration, suggesting the lesions may arise from immune dysregulation. Analysis of stimulated mononuclear cells from an ECD bone lesion from a single patient also demonstrated a proinflammatory microenvironment.

Treatment strategies for ECD have been challenged by rare occurrence and poor understanding of etiopathology. Chemotherapy and corticosteroids effective in LCH and other histiocytic disorders appear to have minimal benefit. However, therapy with interferon-α (IFN-α) has been reported with durable responses in some patients. A rationale for this approach is that IFN-α induces terminal differentiation of some histiocytes and dendritic cells. Targeting interleukin-1 (IL-1), a proinflammatory cytokine expressed by ECD histiocytes, with recombinant interleukin-1 receptor-α (IL-1Ra) has also recently been reported as a promising therapeutic strategy.

In this issue of Blood, Arnaud and colleagues quantitatively analyze 23 cytokines, chemokines, and growth factors in serum samples from 37 patients with ECD. They found many significant differences in cytokine/chemokine levels in ECD patients compared with controls, with principal component analysis identifying an ECD-specific signature based on increased expression of IFN-α, IL-12, monocyte chemotactic protein-1, and decreased expression of IL-4 and IL-7. Compared with controls, untreated patients had...
significantly elevated IL-6, and IFN–treated patients had significantly elevated IL-1Rα. There was no significant difference in cytokine profile comparing ECD patients treated with IFN–α to untreated patients. Furthermore, cytokine profiles were relatively unchanged over months in individual patients on whom serial plasma samples were available. The authors conclude that these data reveal ECD as a condition characterized by specific systemic proinflammatory activation that is not affected by treatment with IFN–α.

Previous studies demonstrated that histiocytes in ECD are clonal, consistent with a neoplastic process. However, the absence of Ki67 cells suggests that they accumulate rather than proliferate within the lesions. In a single patient study, increased cytokine expression (IL-1α, IL-1β, IL-2, and IL-8) was noted in peripheral blood mononuclear subsets by quantitative polymerase chain reaction, demonstrating that cells other than the ECD histiocytes may contribute the proinflammatory plasma cytokine profile. The relative culpability of the ECD lesion histiocytes, peripheral blood dendritic cell precursors, circulating monocytes, or other cells in cytokine production, lesion formation, and disease progression remains to be determined. With this report, Arnaud et al’s study supports a model in which the ECD cytokine microenvironment develops within a complex systemic inflammatory atmosphere. The ECD cytokine signature may provide further clues to pathogenesis as well as tools for diagnosis and targeted therapy.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

REFERENCES

Comment on Allers et al, page 2791

The power of 1 in HIV therapeutics

Raphaëlle Parker and Irini Sereti

In this issue of Blood, Allers and colleagues describe the long-term follow-up of their previously reported HIV + patient who was treated with allogeneic CCR5Δ32/Δ32 stem cell transplantation (SCT) for relapsed acute myeloid leukemia (AML). The patient has since remained off antiretroviral therapy (ART) and without evidence of HIV disease for 45 months after the SCT despite relapse of his AML, which necessitated a second successful transplantation.

During the additional follow-up reported here, CD4 T-cell reconstitution has reached normal values in peripheral blood with 100% donor chimerism as confirmed by absent CCR5 expression. The CD4 T cells of the patient, similarly to other SCT recipients, had a higher proportion of activated effector memory cells and a lower proportion of naive cells compared with healthy controls. CD4 T cell reconstitution was also achieved in the gut mucosa in the reported patient, again to a similar degree as that observed in other SCT recipients. HIV RNA and DNA have not been detected in plasma and several tissues obtained to evaluate symptoms of graft-versus-host disease (GVHD; gut, liver) and leukocencephalopathy (brain). These biopsies showed that tissue macrophages were eventually replaced by donor-derived macrophages lacking CCR5 expression. The T cells of the patient do express normal levels of CXCR4 and appear fully susceptible to X4-tropic HIV in vitro, a relevant observation considering that 2.9% of the isolated viruses before transplantation were X4 or dual-tropic. Finally, HIV-specific antibodies (Ab) continued to wane with only envelope Ab remaining detectable at the end of follow-up.

This single-patient study is important in more than one way. It is hard to prove with certainty the complete eradication of HIV and its latent reservoirs and thus the possibility that residual X4 strains could at some point reactivate and lead to HIV disease progression. Yet it is still reasonable to conclude that CCR5Δ32/Δ32 SCT has probably led to a cure of HIV infection in this particular case. This lends further support to the evaluation of therapeutic strategies that can generate the delta32 phenotype, known to confer resistance to primary infection and slow disease progression in established HIV infection. One of the most encouraging findings of the report is that the SCT allowed over time the replacement of one of the challenging and resilient cells for HIV eradication: the tissue macrophages. This case also highlights how SCT, a high-mortality procedure for HIV + patients in the past, has gained ground with the advent of ART for appropriate underlying diseases. In addition, T-cell reconstitution can be achieved in HIV + patients after SCT, as was recently shown in a series of autologous SCT in HIV patients with relapsed lymphoma.
Erdheim-Chester: beyond the lesion

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