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Saving orphans: BRAF targeting of histiocytosis

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In this issue of Blood, Haroche and colleagues report significant therapeutic activity of the BRAF inhibitor, vemurafenib, in 3 patients with rare histiocytic conditions, Erdheim-Chester disease and Langerhans cell histiocytosis.1

Erdheim-Chester disease (ECD) is the epitome of orphan diseases. The Erdheim-Chester Global Alliance estimates that fewer than 500 cases have been reported in the medical literature since it was first described as a discrete clinical entity in 1930. Although more cases of ECD have been reported in the past decade, diagnosis is challenging because the main pathologic feature of “foamy”-appearing lipid-laden macrophages (histiocytes) can be seen in many other conditions, so identification of ECD rests on the coordinated incorporation of other clinical data, including infiltration of the histiocytes in the retroperitoneum and the curious, near-universal finding of bilateral sclerotic changes in the long bones, most vividly seen on 99Tc-methionine or 18F-fluorodeoxyglucose imaging (see figure).2 Although ECD can be indolent in some patients, in others it can progress inexorably and fatally, often resulting in fibrosis in the heart and the arteries.

Another rare disease, Langerhans cell histiocytosis (LCH), is considered histologically distinct from ECD.1 LCH most commonly affects children, frequently presenting as lytic bone lesions or infiltrative lesions of the skin, lungs, and anterior pituitary. LCH and ECD have a shared history of controversy regarding whether they are reactive, inflammatory conditions or clonal, neoplastic diseases.2,3 Recent studies, however, found that 57% of LCH cases and 54% of ECD patients harbored BRAF V600E mutation in the diseased tissue, strongly suggesting a neoplastic etiology in most cases.4,5

Haroche et al have tested the notion that the BRAF V600E acts as a so-called “driver mutation” of these diseases by treating 3 patients with refractory ECD, 2 of whom had coincident LCH, with vemurafenib, which was recently approved for use in patients with metastatic melanoma characterized by BRAF V600E mutation.1,6 The responses in ECD and LCH were, in the words of the authors, “dramatic.” Two of the 3 patients had symptomatic improvement within days of the initiation of vemurafenib and all 3 patients had significant disease regression after a few weeks of treatment. In the 2 patients who had both LCH and ECD, there was clinical response in both histiocytic conditions. It should be noted that vemurafenib was not without toxicity and all 3 patients required a reduction from the initial dose due to rash, a common side-effect. Further, the dramatic nature of the results must be tempered against the small size of the case series and the short follow up. Median progression-free survival in patients with vemurafenib-treated melanoma was less than 6 months, so the duration of response in the histiocytosis patients will continue to be a point of interest.6

As a corollary to this study, 2 of the 3 patients reported had both ECD and LCH. A few case reports have suggested coincidence of what are considered separate histiocytic entities.7,8 The finding here that both patients had the same BRAF mutation in both histiocytoses with similar therapeutic responses to vemurafenib strongly suggests, by the law of parsimony, a possible developmental link between ECD and LCH. As evidence mounts that most cases of LCH are clonal and neoplastic, and that the cell of origin is most likely an immature myeloid dendritic cell rather than a mature tissue-based dendritic cell,3,9 the coincidence of the rare LCH with the ultra-rare ECD might prompt re-examination of the connection between these 2 conditions.

These results will surely come as welcome news to the devoted cadre of physicians who care for this collection of rare diseases as well as the patients who suffer from them. At present, the best-established treatment of ECD is interferon and standard therapies of LCH use cytotoxic agents.3,10 Thus, a targeted treatment
Demethylation demystification

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The ability of the DNA methyltransferase inhibitors (DNMTi) to induce terminal differentiation in fibroblasts was first noted by Taylor and Jones in 1979; Silverman and Holland reported hematologic improvement in patients with myelodysplastic syndrome (MDS) in 1993. That azacitidine improves survival in patients with high-risk MDS and acute myeloid leukemia with MDS features compared with a combined comparator group of supportive care, low–dose cytarabine, and intensive cytarabine plus anthracycline, while inducing trilineage normalization in approximately 15% of patients makes the development of more potent, more specific drugs that behave like azacitidine imperative. The question is, how do the azanucleosides behave? That cellular and clinical responses derive from a change in gene expression patterns resulting from promoter methylation reversal.

The problem is that such an association has been difficult to demonstrate. Several studies investigating changes in global methylation, methylation and/or expression of specific target genes, and genome–wide methylation and/or expression in patients receiving deoxyazacytidine (DAC) or 5-azacytidine (5AC), alone or in combination with other drugs, have failed to discriminate clinical responders from clinical nonresponders on the basis of baseline methylation/expression parameters or changes in these metrics (see figure). Measurable changes in methylation appear necessary for clinical response (no doubt as a marker of drug bio-availability and adequate concentration) but have not been shown to be sufficient or mechanistically linked. These studies may be critiqued on the basis of the methodologies used, the times at which the tumor was sampled, and the heterogeneity of the patients treated.

In this issue of Blood, Klco and colleagues treat primary acute myeloid leukemia bone marrow samples with DAC in a stromal coculture system for 3 days before analyzing changes in the methylene and expression profiles. Methylation array data showed high methylation levels in some promoters, but also in gene bodies and untranslated regions. Furthermore, decitabine induced hypomethylation–favored areas with higher baseline methylation and extent of methylation reversal appeared to correlate with degree of initial methylation. Thus, methylation changes were frequently more extensive in gene bodies than in CpG islands, similar to a recent study by Yan et al. Post-mock and Post-DAC treatment samples of each leukemia cluster with themselves in unsupervised analysis, rather than with other treated samples, and correlation between changes in methylation and gene expression was “subtle,” and did not apply to CDH1 or CDKN2B, 2 frequently methylated tumor suppressor genes in myeloid neoplasms.

This well-done study by Klco et al parallels the clinical experience, demonstrating a lack of demonstrable direct connectivity between methylation reversal events in response to azanucleosides and canonical early changes in gene expression. It is therefore not surprising that connecting such changes to clinical responses that manifest several months later has
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