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Ozlem Goker-Alpan and Ellen Sidransky

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● ● ● CLINICAL OBSERVATIONS

Comment on Rosenbloom et al, page 4569

# Risky business: Gaucher disease and multiple myeloma

Ozlem Goker-Alpan and Ellen Sidransky NATIONAL INSTITUTE OF MENTAL HEALTH; NATIONAL HUMAN GENOME RESEARCH INSTITUTE

In this issue, Rosenbloom and colleagues studied whether patients with Gaucher disease have an increased risk of malignancies. Their results, based on an international patient registry, suggest that the cancer rate—with the exception of multiple myeloma—is not elevated.

As both the life expectancy and spectrum of phenotypes associated with Gaucher disease are extended, there is increased concern among patients and physicians regarding the possible association of glucocerebrosidase deficiency with other life-threatening or debilitating illnesses. Examples include small subsets of adult patients who develop either pulmonary hypertension<sup>1</sup> or parkinsonism.<sup>2</sup> Another concern, based on information in earlier publications, is of an increased risk for various cancers, especially

hematologic malignancies.<sup>3</sup> In each of these cases, the associated disorder may be more frightening than type 1 Gaucher disease itself.

In this issue of *Blood*, Rosenbloom and colleagues study a larger cohort of patients with Gaucher disease, albeit one with inherent biases, and conclude that multiple myeloma is the only malignancy observed at an increased frequency, with an estimated relative risk of 5.9. This leads to a mixed “good news/bad news” message: we can stop worrying exces-

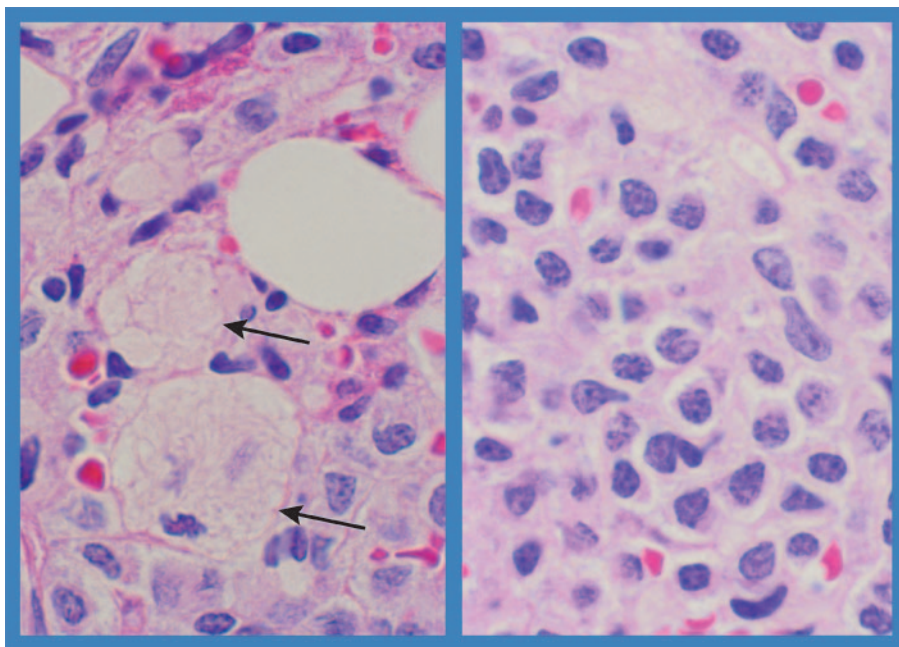
sively about most cancers, but the association with myeloma is reinforced.

Are these associated adult-onset disorders part of the natural history of Gaucher disease, or does abnormal glucocerebrosidase serve as an additional risk factor in individuals who are otherwise prone to developing these illnesses? The answer is not so straightforward. Among individuals who develop parkinsonism, mutations in glucocerebrosidase appear to be only one contributing risk factor. This is supported by the evidence that, whereas the vast majority of patients with Gaucher disease never develop parkinsonian manifestations, parkinsonism in some families is more prevalent among Gaucher carriers and patients, although there is incomplete penetrance. Conversely, there is an increased frequency of heterozygosity for glucocerebrosidase mutations in cohorts of patients with sporadic Parkinson disease.<sup>2</sup>

What about multiple myeloma? The existence of an association between Gaucher disease and this malignancy, a plasma cell neoplasm characterized by production of monoclonal immunoglobulin, has been known for some time. The important role of macrophages in the pathogenesis of Gaucher disease and reports of abnormalities of both B and T cells have led to speculation about the contribution of immune activation. In Gaucher disease, elevated levels of proinflammatory cytokines, particularly interleukin 6 (IL-6), may correlate with clonal expansion of B cells.<sup>4</sup> IL-6 is the major cytokine involved in the growth and survival of myeloma cells, and its secretion is up-regulated by CD40 activation.<sup>5</sup> Regulation of this system involves complex interactions between many genetically determined cofactors.

The biologic and clinical behavior of myeloma cells is not exclusively determined by their genetic background; it is also influenced by the bidirectional relationship with the bone marrow, which provides a microenvironment in which myeloma cells can survive and induce bone marrow resorption through osteoclast activation.<sup>5</sup> In Gaucher disease, the skeletal lesions reflect an imbalance in this system and are part of the disease course.

Thus, the increased frequency of multiple myeloma found by Rosenbloom et al may reflect the interplay between the natural history



**Bone marrow histology in a patient with Gaucher disease and multiple myeloma. Bone marrow biopsy obtained at the time of diagnosis of multiple myeloma in a 56-year-old male patient with Gaucher disease. (Left panel) Small areas containing Gaucher cells (arrows). (Right panel) Extensive infiltration with abnormal plasmacytoid lymphocytes and plasma cells (hematoxylin and eosin; original magnification  $\times 1000$ ; Olympus BH-2). Immunostaining was positive for CD38, immunoglobulin G, and lambda. Karyotyping revealed no chromosomal rearrangements. (Courtesy of Dr Margaret E. Rick, Hematology Service, Department of Laboratory Medicine, Clinical Center, National Institutes of Health, Bethesda, MD.)**

of Gaucher disease and as-yet unknown genetic risk factors for the development of gammopathies in some patients. The difficulties in determining the genetic and mechanistic bases for this association highlight the complexities of this “simple” Mendelian disorder. ■

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## NEOPLASIA

Comment on De Keersmaecker et al, page 4849

# A remark ABL new fusion oncogene in T-cell ALL

Richard A. Van Etten TUFTS-NEW ENGLAND MEDICAL CENTER

A novel fusion of *ABL1* to *EML1* adds to a growing list of chimeric ABL proteins in patients with acute T-cell lymphoblastic leukemia.

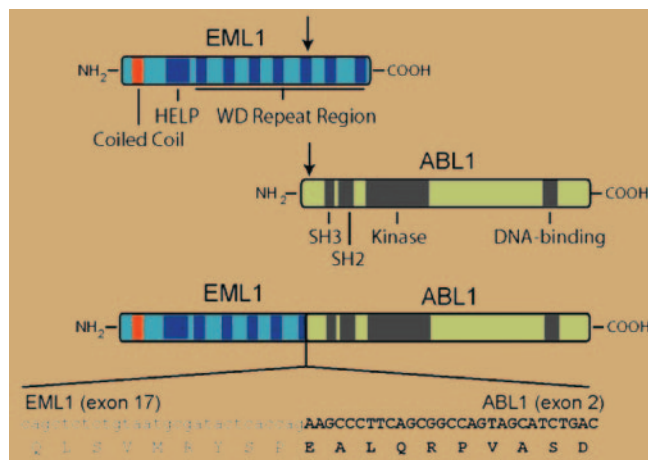
Until recently, our recognition of the involvement of the *ABL1* gene (which encodes the nonreceptor protein tyrosine kinase c-ABL1) in the pathogenesis of T-cell acute lymphoblastic leukemia (T-ALL) was limited to rare cases of Philadelphia chromosome-positive T-ALL, some of which likely represented lymphoid blast crisis of chronic myeloid leukemia. The first hint that *ABL1* might be involved more frequently in this disease came from a United Kingdom Medical Research Council study that used fluorescent in situ hybridization (FISH) with probes from the *ABL1* locus to analyze interphase nuclei from lymphoid leukemia blasts. The study was intended to detect cryptic *BCR-ABL1* fusion but instead found extrachromosomal amplification of the *ABL1* locus independent of *BCR* in 8 of 280 T-ALL samples.<sup>1</sup> The nature of the amplification was soon revealed when researchers from the University of Leuven in Belgium demonstrated that *ABL1* was fused to *NUP214* via episomal amplification in 5 of 90 patients with T-ALL.<sup>2</sup> This resulted in fusion of N-terminal sequences of the NUP214 protein, a ubiquitously expressed component of the nuclear pore complex, with the same 1104 C-terminal amino acids of c-ABL1 found in the BCR-ABL1 fusion protein. Like BCR-ABL1, the NUP214-ABL1 fusion is a constitutively active tyrosine kinase

with transforming activity in vitro. Collectively, these results suggested that *ABL1* might be involved in the pathogenesis of 5% to 6% of T-ALLs.

In the current issue of *Blood*, the Leuven group extends these results to identify a new *ABL1* fusion gene in T-ALL. A patient with T-ALL whose blasts lacked *ABL1* amplification but demonstrated a split in the hybridization signal between 5' and 3' *ABL1* probes was found to have cryptic t(9;14), leading to fusion of *ABL1* with *EML1* on chromosome 14. *EML1* encodes a protein with similarity to an echinoderm microtubule-associated protein (EML1), and the resulting 190-kDa echinoderm microtubule-associated protein-like 1-Abelson 1 (EML1-ABL1) fusion is a dysregulated tyrosine kinase that alleviates interleukin-3 dependence in Ba/F3 hematopoietic cells and constitutively activates extracellular signal-

related kinase (ERK), signal transducers and activators of transcription 5 (Stat5), and Src signaling pathways. As with BCR-ABL1, EML1-ABL1 kinase activity was dependent on a coiled-coil domain in the N-terminus, suggesting that oligomerization and autophosphorylation are necessary to overcome the autoinhibition of the ABL kinase domain.<sup>3</sup> The leukemic cells from this patient exhibited ectopic expression of the homeobox transcription factor TLX1 and hemizygous deletion of the *CDKN2A* tumor suppressor gene. These alterations were also seen frequently in patients with *NUP214-ABL1* fusion<sup>2</sup> and provide more evidence that T-ALL can be divided into subgroups with distinct molecular pathogenesis.<sup>4</sup> Interestingly, expression of *EML1* was not observed in other T-ALL blasts or cell lines, suggesting that the *EML1* promoter may be activated as a consequence of the translocation.

These findings have therapeutic implications, of course. The EML1-ABL1 fusion protein was inhibited by imatinib mesylate, the small molecule inhibitor of ABL kinase activity, with approximately the same sensitivity as BCR-ABL1, raising the possibility that patients with T-ALL with NUP214-ABL1 and EML1-ABL1 might respond clinically to imatinib treatment. In the previous study, imatinib was found to inhibit the growth of a T-ALL cell line with the NUP214-ABL1 fusion,<sup>2</sup> but the clinical utility of imatinib in these patients might be limited by rapid selection for resistance, as is observed in Philadelphia chromosome-positive patients with



In T-ALL with cryptic t(9;14), N-terminal sequences from the EML1 polypeptide, including a coiled-coil domain, are joined to the same C-terminal ABL sequences present in the more common BCR-ABL1 fusion protein. The resulting 190-kDa EML1-ABL1 fusion protein is a dysregulated tyrosine kinase that transforms Ba/F3 cells. For details, see the article beginning on page 4849.