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Letters to Blood

TO THE EDITOR:

MGUS, lymphoplasmacytic malignancies, and Gaucher disease: the significance of the clinical association

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Despite the astounding twenty-first century growth in informatics science and technology, individuals with rare disorders often continue to suffer morbidity and anxiety as a result of inaccurate diagnosis or delayed treatment.[1] Although 86% of patients with Gaucher disease (GD) see a hematologist before diagnosis,[2] only 20% of surveyed hematologists worldwide initially thought of this condition when presented with a hypothetical case scenario of a patient presenting with all 6 of the most common GD signs and symptoms.[3] Subsequently, we have had many opportunities to participate in live and Web-based educational programs to boost awareness about GD. This disorder has highly effective treatments available when indicated, but affected individuals with apparently mild phenotypes are nonetheless at increased risk for late-onset concurrent illnesses such as Parkinsonism, hematologic malignancies (especially B-cell lymphoplasmacytic lymphoma), and hepatocellular carcinoma.[4,5]

Therefore, when reading the recent highly informative article "How I manage monoclonal gammopathy of undetermined significance,"[6] in *Blood*, we noticed with some chagrin that GD was not even mentioned in a fairly long list of concurrent conditions with which monoclonal gammopathy of undetermined significance (MGUS) has been associated. In fact, MGUS in association with GD was described as long ago as 1968,[7] and it is now well recognized that the risk for myeloma in affected individuals may be 25- to 50-fold greater than expected in the general US and European populations.[8] Furthermore, we now know that the monoclonal antibodies found in GD patients with MGUS and myeloma are specifically directed at macrophage CD1d-presented glycosphingolipid antigens.[9] This observation strongly supports the hypothesis that attributes GD-associated gammopathy to somatic mutations driven by chronic immune stimulation abetted by inflam-matory cytokines.[10,11]

The risk of Parkinsonism is increased in both GD patients and heterozygous carriers of *GBA1* mutations because mutant misfolded glucocerebrosidase itself seems to contribute to α-synuclein aggregation in dopaminergic neurons.[12] But there is no evidence that GD carriers, who do not seem to accumulate pathogenic sphingolipids, have an increased risk for MGUS and myeloma.[13] Although GD-specific intravenous enzyme replacement therapy does not seem to reverse monoclonal gammopathy once it is established,[14] we do not yet know whether early initiation of either enzyme replacement therapy or oral substrate synthesis inhibition therapy before the emergence of malignant plasma cell clones will be preventive. However, inhibition of glucosylceramide synthase does seem to prevent GD-associated B-cell malignancy in Gaucher mouse models.[9,15] It is also unknown whether the coexistence of GD and MGUS accelerates the usual 1%-per-year risk of MGUS evolving to overt myeloma.[6] Because of the small number of patients, there is no established treatment paradigm, and there is little published information about treating GD-associated myeloma regarding either efficacy or toxicity of current immunomodulatory myeloma regimens or autologous hematopoietic stem cell transplantation.

We are aware of patients who were initially diagnosed with MGUS or myeloma in whom GD was discovered coincidentally. For that reason, we urge hematologists to consider the possibility of concurrent GD in patients they manage for MGUS, myeloma, Waldenström macroglobulinemia, AL amyloidosis, and B-cell lymphoma, especially, but not exclusively, in patients of Ashkenazi Jewish ethnicity. In Ashkenazi Jewish patients, the incidence of genotypic GD is as high as 1 in 500, and they may be middle age or older without overt signs or symptoms of GD. Testing for GD by assaying peripheral white blood cells or dried blood spots for the presence of β-glucosidase or glucosylsphingosine is widely available.[16,17] Identification of apparent Gaucher cells in the bone marrow may not necessarily be pathognomonic because pseudo Gaucher cells have occasionally been reported in myeloma patients.[18] Nevertheless, a finding of Gaucher cells should prompt a diagnosis of GD unless proven otherwise. It is also wise to point out that GD bone marrow infiltration is sometimes associated with abnormal positron emission tomography scanning that could be misinterpreted as myeloma bone disease[19,20] and could lead to erroneous upstaging.

We urge hematologists who are managing GD patients with or without hematologic malignancies to participate in international and national GD registries (eg, www.clinicaltrials.gov and www.gaucherdisease.org/research/registry). These databases may be the only research tools that have sufficient power and patient numbers to provide strong evidentiary guidance about managing and treating this rare disorder and ultimately, preventing its long-term complications.[21,22]

Authorship

Contribution: N.J.W. conceived and drafted the letter; and P.K.M., B.E.R., and M.V.D. edited the text.

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TO THE EDITOR:

Detection of clonal hematopoiesis of indeterminate potential in clinical sequencing of solid tumor specimens

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Clonal hematopoiesis of indeterminate potential (CHIP) describes an expansion of hematopoietic stem cells that harbor somatic mutations[1-5] without an underlying hematologic malignancy or definitive morphologic evidence of dysplasia.[6] CHIP can evolve to overt neoplasia, with a progression rate of 0.5% to 1.0% per year.[2,3] CHIP was first identified through genomic profiling of peripheral blood from healthy individuals.[1-5] Its incidence increases with age and has been detected in peripheral blood of patients with solid tumors.[7,8] In elderly cancer patients, the presence of CHIP prior to chemotherapeutic exposure is