higher proportion of patients can be recognized as having a low-grade lymphoma with low tumor burden. One deficiency of the current article is that it is based on registry data, and there was inconsistent analysis of the patients' bone marrow, which makes the reported frequency with which lymphoma coexists suspect.

Cryoglobulinemia is a form of systemic vasculitis. The immune complex consisting of the monoclonal protein, polyclonal immunoglobulin, and complement deposits diffusely on endothelial surfaces, and the complement activation causes endothelial damage. The most common clinical manifestations are purpura, edema, neuropathy, and glomerulonephritis. In more advanced situations, livedo reticularis and cutaneous ulcers develop (see figure). Patients presenting with isolated purpura do not require systemic therapy. Purpura can be managed by support hose, and the purpura is primarily a cosmetic concern. Involvement of the kidneys leading to proteinuria and active urinary sediment manifests histologically as membranoproliferative glomerulonephritis or vasculitis-driven cutaneous ulcers require urgent therapy. Corticosteroids have been the mainstay of treatment of systemic vasculitis because of cryoglobulinemia and are effective. Responses can occur within 72 hours, but many patients become corticosteroid dependent. Rituximab was reported to be an effective therapy over 10 years ago, but until this issue of Blood sufficient numbers of patients had not been treated to comparatively assess its efficacy.

The lymphocytes producing the IgM monoclonal protein are expected to strongly express CD20; thus the use of rituximab in this disorder is logical. At the Sixth International Workshop for Waldenström macroglobulinemia, this disorder is logical. At the Sixth International Workshop for Waldenström macroglobulinemia, the complement deposition was considered a variant of Waldenström macroglobulinemia characterized by IgM-mediated symptoms. The activity of rituximab in Waldenström macroglobulinemia is well-recognized, the expectation that rituximab would provide benefit in type II cryoglobulinemia is reasonable.

Immunologic derangements have been described with cryoglobulinemia including a decreased percentage of naive B-cells and CD4-positive, CD25-positive, FOXP3-positive regulatory T cells. These immunologic abnormalities revert after rituximab therapy. It is unlikely that prospective randomized trials of the therapy of nonhepatitis-associated cryoglobulinemia will ever occur. It is reasonable to consider rituximab and corticosteroid the default standard of therapy for patients who do not have evidence of frank lymphoma and require therapy.

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Comment on Pagel et al, page 6016

Are all mutant SNAREs equal?

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In this issue of Blood, Pagel et al1 carefully delineate some fascinating phenotype/genotype correlations in a larger cohort than in their earlier reports of familial hemophagocytic lymphohistiocytosis (HLH).2,3

The protein coded for by STXBP2, MUNC18-2 impacts the formation and dissolution of SNARE (soluble N-ethylmaleimide sensitive factor attachment protein receptor) complex and the control of membrane fusion. Of 37 FHL5 patients evaluated, 24 had no exon 15 splice site mutations and 13 had them. The phenotype differences were striking (see Table 4 on page 6021 of the article by Pagel et al). Those with the exon 15 splice site mutations were older and had a different profile of unique clinical characteristics from those without the splice site mutations. A proline-leucine change at P477L leads to no STXBP2 expression and early onset of HLH.

MUNC18-2 protein controls T-cell toxicity but also impacts immunoglobulin synthesis, platelet function, and intestinal motility or absorption as found in B cells, epithelial tissues, kidney, and intestine. Some of the concepts used to understand MUNC18-2 come from studies of the STXBP2/H9254 granulocyte protein receptor complex and the control of membrane fusion. Of 37 FHL5 patients, 24 had no exon 15 splice site mutations and 13 had them. The phenotype differences were striking (see Table 4 on page 6021 of the article by Pagel et al). Those with the exon 15 splice site mutations were older and had a different profile of unique clinical characteristics from those without the splice site mutations. A proline-leucine change at P477L leads to no STXBP2 expression and early onset of HLH.

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HLH patients with 48% having a A91V-ORF1 genotype. Horne et al found a higher prevalence of perforin mutations in patients from the Middle East and syntaxin mutations in Turkish patients compared with Nordic patients. They found no differences in presenting signs and symptoms based on genotype, but reported that patients with perforin mutations presented at median age of 2.3 months, MUNC mutations 6.2 at months, and syntaxin mutations at 14.4 months. Central nervous system disease was more prevalent in patients with perforin mutations versus syntaxin mutations. Ueda et al found that of 40 FHL patients, those with non-sense perforin mutations (FHL2) had higher sIL-2 receptor and ferritin levels and presented after 7 years of age.

The work by Pagel et al is the result of well-organized collaborations over many years and shows the power of translational research to better inform us about a rare disease and basic biology. As more mutations in the FHL-associated genes are cataloged we may well learn of other genotype/phenotype associations. One of the important offshoots of this work is that clinicians may now start thinking about HLH in patients who have chronic diarrhea, hypogammaglobulinemia, platelet function defects, and sensorineural hearing defects and develop cytopenias, fever, elevated ferritin, or other signs of this syndrome.

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