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 co-exists 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 up until this time 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 Waldenstro¨m macroglobulinemia, it was reaffirmed that cryoglobulinemia is reasonable.9 At the Sixth International Workshop for Waldenstro¨m macroglobulinemia, it was reaffirmed that cryoglobulinemia was considered a variant of macroglobulinemia, and it was reaffirmed that cryoglobulinemia is reasonable.

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 up until this time 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 Waldenstro¨m macroglobulinemia, it was reaffirmed that cryoglobulinemia was considered a variant of macroglobulinemia, and it was reaffirmed that cryoglobulinemia is reasonable.

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 up until this time 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 Waldenstro¨m macroglobulinemia, it was reaffirmed that cryoglobulinemia was considered a variant of macroglobulinemia, and it was reaffirmed that cryoglobulinemia is reasonable.

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 up until this time 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 Waldenstro¨m macroglobulinemia, it was reaffirmed that cryoglobulinemia was considered a variant of macroglobulinemia, and it was reaffirmed that cryoglobulinemia is reasonable.

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 up until this time 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 Waldenstro¨m macroglobulinemia, it was reaffirmed that cryoglobulinemia was considered a variant of macroglobulinemia, and it was reaffirmed that cryoglobulinemia is reasonable.

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 up until this time 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 Waldenstro¨m macroglobulinemia, it was reaffirmed that cryoglobulinemia was considered a variant of macroglobulinemia, and it was reaffirmed that cryoglobulinemia is reasonable.
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.

Conflict-of-interest disclosure: The author owns common stock in Johnson & Johnson and receives research support from the National Institutes of Health and clinical trial support from Glaxo Smith Kline.

REFERENCES
6. Verhege M, Maas AS, Plomp JJ, et al. Synaptic assem-
Are all mutant SNARES equal?

Kenneth L. McClain