Comment on Wechalekar et al, page 3420

Allaying and alleviating amyloid agony and anxiety

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1MAYO CLINIC

In this issue of Blood, Wechalekar and colleagues demonstrate the importance of treating all patients with amyloidosis, no matter how severe their situation is, because clinically important responses are seen.1 They also identify the adverse prognostic impact of a systolic blood pressure of <100 mm Hg.1

This article from the 4 largest amyloidosis centers in Europe is important because it reports on large numbers and reduces the referral biases that major medical centers see with these patients. Often, when patients present with advanced end-stage disease, they are not referred or do not survive to be seen in a center of expertise, and reported center outcomes are not reflective of an unselected population. Moreover, these patients are often excluded from clinical trials of therapy in amyloidosis. As a result, published phase 2 trials are not representative of the “real-world” situation with amyloidosis.2 All patients in this report were cardiac stage III3 defined by an amino-terminal fragment brain-type natriuretic peptide (NT-proBNP) of >332 ng/L and a cardiac troponin T of >0.035 μg/L or a cardiac troponin I >0.1 μg/L. These patients do poorly in large part due to late diagnosis and an inability to aggressively treat patients with poor performance status. Patients with cardiac amyloidosis are often diagnosed late because the condition is a classic example of heart failure with preserved systolic function and normal ejection fraction.4 Physical findings such as purpura and enlargement of the tongue (see figure) are useful when present but are generally absent in 85% of patients, so a high index of suspicion is required.

A number of staging systems exist to help prognosticate outcomes in amyloidosis, most recently, a combination of cardiac biomarkers and the difference between involved and uninvolved immunoglobulin free light chains, a measure of tumor mass.5 For patients with advanced cardiac failure, the severity of heart impairment eliminates the relevance of the free light chain from the statistical model. A systolic blood pressure of <100 mm Hg, reflecting advanced stiffening of the heart, poor diastolic filling, and a reduced stroke volume, resulting in a reduced systolic blood pressure, carries paramount importance in predicting outcome. Even with the poor prognosis in this group, the overall hematologic response rate on an intent-to-treat basis was 33% with 12% complete responses. It appears that no patient with amyloidosis should be denied a trial of therapy. The number of patients in each treatment category does not allow selection of any superior therapy: patients responded to combinations of melphalan and dexamethasone; combinations using thalidomide; and combinations using either bortezomib, lenalidomide, or both. A small subset of responders may become suitable candidates for safe stem cell transplantation6 with reported 10-year survivorship.7

Hematologists that see patients with monoclonal gammopathy of undetermined significance must be on the lookout for amyloidosis, which can manifest as simple fatigue or weight loss and be misattributed to multiple myeloma, simply because the bone marrow shows 10% plasma cells. Over 25 years of monitoring, one-quarter of patients with monoclonal gammopathy of undetermined significance will develop a serious plasma cell proliferative disorder. What is often overlooked is that one-eighth of these patients, or ~3%, will develop light...
chain amyloidosis. This can occur without a rise in the size of the monoclonal protein, and the monitoring physician must be aware of the development of diarrhea, edema, or lower extremity paresthesias. Others have suggested that measurement of the NT-proBNP become part of the evaluation of patients with monoclonal gammapathy of undetermined significance who are being observed to detect early amyloid cardiomyopathy.

Amyloidosis is rare, and because no specific diagnostic test exists, lacking a high index of suspicion, it can easily be overlooked. The responses to chemotherapy reported in this manuscript clearly benefit our patient population even with advanced cardiac disease. The development of new agents for the treatment of amyloidosis include pomalidomide, the potential for carfilzomib, MLN-9708, and the exciting development of amyloid-specific monoclonal antibodies offers great hope for the future of our patients.

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REFERENCES

Presenting ADAMTS13 on a TTP-associated MHC

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In this issue of Blood, Sorvillo et al investigate possible molecular triggers leading to idiopathic, autoimmune thrombotic thrombocytopenic purpura (TTP) by identifying naturally processed A Disintegrin And Metalloprotease with ThromboSpondin type 1 motif 13 (ADAMTS13)-derived peptides presented on human dendritic cells.

TTP is a rare but serious pathological disorder in which the ultra large form of von Willebrand factor (ULVWF) released by activated endothelium into the circulation cross-links platelets, causing intravascular agglutination under high shear stress, ie, primarily in the microvasculature. Most patients with idiopathic TTP have acquired autoantibodies to ADAMTS13, a large circulating metalloprotease that cleaves ULVWF at a specific site, generating VWF multimers that are significantly less adhesive than ULVWF. Anti-ADAMTS13 antibodies in plasma from TTP patients consist primarily of IgG4 and IgG3 subclasses, indicating the involvement of effector T cells in the etiology of this disease, and the major histocompatibility complex (MHC) allele HLA-DRB1*11 has recently been identified as a risk factor for the development of TTP. The study by Sorvillo et al presented in this issue systematically investigated the HLA restriction of ADAMTS13 peptide presentation on human MHC Class II by isolating and expanding dendritic cells from 17 healthy blood donors in culture, “feeding” them different concentrations of recombinant ADAMTS13 protein, and then recovering the peptides presented on their surface and identifying them using mass spectrometry. Interestingly, dendritic cells exposed to ADAMTS13, but not control cells treated with phosphate-buffered saline alone, presented peptides derived from several ADAMTS13 domains, and peptides derived from its C-terminal CUB2 domain were presented with the highest efficiency. Dendritic cells from donors with an HLA-DRB1*11 allele exposed to a higher ADAMTS13 concentration presented only differentially processed versions of the same CUB2 peptide, which contains the predicted DRB1*11-binding sequence FINVAPHAR. The binding of naturally processed ADAMTS13 peptides to MHC Class II on human dendritic cells indicates that these peptides may contain clinically relevant T-cell epitopes, although future experiments showing stimulation of human effector T cells by similar peptides will be required to confirm this hypothesis.

Autoimmune TTP is caused by antibodies that bind to ADAMTS13 and neutralize its proteolytic activity. Most acquired TTP patients circulate antibodies that bind to the spacer domain of ADAMTS13, although antibodies with specificity for other regions, including the CUB domains, have also been identified in subsets of TTP patients. Although T-cell and B-cell epitopes often occur in close proximity or even overlap, they can also be derived from spatially distant regions of a protein antigen. This is because the presentation of T-cell and B-cell epitopes to the immune system is fundamentally different. CD4 T-cell epitopes consist of peptides at least 9 to 16 residues in length derived from antigens such as ADAMTS13, which bind to the MHC Class II binding groove on antigen-presenting cells. The MHC Class II–peptide complex is presented to T-cell receptors on, presumably in the case of TTP, autoreactive T cells that escaped thymic deletion and subsequently became
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