Comment on Stangou et al, page 2998

Fibrinogen amyloidosis: the clot thickens!

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In this issue of Blood, Stangou et al discuss a possible role for hepatorenal transplantation in the management of patients with fibrinogen amyloidosis, based on a detailed evaluation of 22 patients, the largest group to date. The authors also considerably expand the current phenotypic description of fibrinogen amyloidosis, including their interpretation of previously unrecognized disease manifestations and risks.

Amyloidoses are disorders of protein folding that result in the formation of fibrillar deposits with a characteristic affinity for Congo red dye and a characteristic appearance by electron microscopy. These deposits are associated with organ damage, and an ever-expanding number of different proteins have been shown to be implicated in amyloid deposition and pathology. Although the precise mechanism of amyloidogenesis is not yet fully understood, it is proposed that characteristics of the primary structure of deposited proteins render them amyloidogenic. The most common type of systemic amyloidosis (AL) is characterized by deposition of clonal immunoglobulin light chains and is associated with plasma cell dyscrasias, from monoclonal gammopathies through full-blown multiple myeloma. The second most common type, termed AA, is linked to deposition of a serum precursor protein SAA, which is typically produced at high levels in certain inflammatory responses. In recent years, yet another group of systemic amyloidoses has emerged associated with genetic defects in amyloid-forming proteins including transthyretin, fibrinogen, lysozyme, and others.

The available treatments for systemic amyloidoses target the supply of the amyloidogenic proteins. Thus, in AL, a durable response can be achieved by chemotherapy or targeted therapies directed at clonal plasma cells, whereas in AA, control of the underlying inflammatory condition is attempted. In a subset of hereditary amyloidoses, where the liver is the exclusive (or predominant) source of abnormal protein, liver transplantation has been used as an approach to remove the site of production of the pathologic protein. Fibrinogen amyloidosis (AFib), discovered more than 15 years ago, is amyloid deposition occurring due to the presence of a variant of fibrinogen, which is produced exclusively by the liver. AFib is the most common type of hereditary amyloidosis in Europe and possibly also in the United States. Until recently, information about this disease was limited to case reports. However, the recent publication by Gillmore and colleagues was the first attempt to define the phenotype of AFib based on an evaluation of a large patient series (71 patients). Based on analysis of the genetic and clinical findings, these authors confirmed earlier reports concluding that AFib is associated with a relatively slow progression of amyloid deposition, compared with the more common AL, and the target organ is predominantly the kidney. Although these authors noted a high prevalence of atherosclerotic cardiovascular disease among their AFib patients, they concluded that it was comparable to that seen in patients with chronic kidney disease in general, and thus secondary to this process.

In this issue, Stangou and colleagues extend the literature in 2 significant ways. First, they describe a high incidence of previously unreported visceral, vascular, cardiac, and neurologic involve in AFib. They conclude that AFib is not solely nephropathic, but...
is a more systemic disease with a diverse and complex phenotype. In particular, they believe that cardiovascular amyloidosis appears to be underdiagnosed. In the affected persons, the authors found a high incidence of cardiovascular atheromatous disease predating the evolution of proteinuria or renal impairment by many years; there was also a strong family history of coronary/vascular disease in these patients. The authors document deposition of a fibrillogen variant in vascular walls and in atheromatous plaques, thus linking variant fibrillogen amyloidosis and atherosclerosis. They conclude that the cardiovascular findings are unlikely to be due solely to renal failure, in contrast to Gillmore et al.4 Stangou et al suggest that direct amyloid deposition in vascular walls may be the first step in a disease process that leads to impaired endothelial function, and that nephrotic syndrome with hyperlipidemia and hypertension may then facilitate atheroma formation (see figure). If this is indeed confirmed by further studies, this hypothesis will associate yet another type of amyloidosis (ie, in addition to AA, AAp-o-AI, and AAp-o-AII) with atherosclerosis. These findings may be relevant to the care of AFib carriers and nonscreened family members.

The second major focus of the paper is reporting the results of hepatorenal transplantation in a subset of these patients. This approach is predicated on the authors’ belief that AFib is a systemic and serious disorder, affecting more organs than solely the kidneys, and that therefore renal transplantation can be compromised by ongoing damage to other tissues and to the new renal graft. In their series of hepatorenal transplant recipients, the authors report a halt in the progression of amyloid deposition, and some evidence for improvement in pretransplantation symptoms, including gut dysmotility. Because hepatorenal transplantation appears to prevent disease progression and allow reversal of some organ dysfunction, the authors advocate early or even preemptive transplantation of liver alone, that is, before renal failure and significant cardiovascular amyloidosis develop, especially because the latter may preclude transplantation. This is certain to be a contentious issue, but Stangou et al provide important data to consider in designing the best approach for individual patients.

Phenotype variability is well known in transthyretin amyloidosis and largely depends on the type of mutation. With 6 amyloidogenic mutations in the fibrillogen A α-chain reported to date, and the discovery of considerable phenotypic variability, the possibility of a similar phenotype/genotype relationship in AFib also appears probable. The cohort size in studies to date precludes detailed phenotype/genotype conclusions, but it is likely that in the future, specific mutations may be linked to variations in disease penetrance and progression.

While the clinical spectrum of the amylol- oses and their available therapies are evolving, the important message to the readership of Blood is that diagnosis of amyloidosis must be sought early in the disease process and its type determined correctly. It should never simply be “assumed” to be AL.

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REFERENCES

CLINICAL TRIALS

Comment on Dunleavy et al, page 3017, and Sparano et al, page 3008

HIV-associated lymphoma

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The role of infusional chemotherapy and the value of rituximab with chemotherapy have not been clearly defined in patients with HIV–associated lymphoma. Recent data have provided insights into these questions.

Although the optimal therapeutic strategies for patients with HIV–associated lymphoma have remained controversial, recent studies by Dunleavy et al and Sparano et al in this issue of Blood have brought clarity to several contentious issues.1,2 First, should rituximab be included within the regimen? Second, does the benefit of a prolonged infusion, such as the EPOCH regimen,3 outweigh the inconvenience and cost? Third, should antiretroviral therapy be suspended during chemotherapy? Fourth, are there subtypes of lymphomatous disease that should be treated differently than others? Fifth, is FDG-PET scanning a useful restaging and prognostic tool in HIV lymphoma?

The addition of rituximab to the CHOP regimen has resulted in remarkable prolongation in long-term disease-free survival among patients with HIV-negative diffuse large B-cell lymphoma (DLBCL),4 and early results among patients with HIV–associated lymphoma appeared also to show benefit.5 Unexpectedly, a randomized phase 3 study of CHOP with or without rituximab, performed by the AIDS Malignancy Consortium (AMC), found only a trend toward greater efficacy in patients on the rituximab arm, with a statistically significant increase in death due to infection.6 When analyzed more carefully, these infectious deaths occurred primarily among patients with severe immunodeficiency. If patients with CD4 lymphocyte counts less than 50/μL were excluded from the analysis, no significant difference in infectious death was seen. Severe HIV–related immunodeficiency in itself has been associated with an increased risk of septic death, even in the absence of chemotherapy.7 Nonetheless, rituximab has been associated with various viral infections, as well as progressive multifocal leukoencephalopathy and hepatitis B reactivation, and could theoretically be a concern.8 The results of the AMC study served to emphasize these concerns, and was in all likelihood responsible for a change in treatment paradigm away from the use of rituximab in HIV–infected patients. In this issue of Blood, a subsequent randomized phase 2 study from the AMC did not show an increased risk of

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