Diagnosis and workup of the patient with amyloidosis

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Patients with Waldenström macroglobulinemia may develop symptomatic AL amyloidosis, and in primary amyloidosis an underlying IgM clone is responsible for the diseases in 7% of subjects. The presence of amyloid-related organ dysfunction poses peculiar challenges in the diagnostic workup and treatment of these patients and needs to be detected before irreversible damage ensues. While clinical signs and symptoms are usually late, biomarkers of cardiac and renal involvement, such as elevated concentrations of N-terminal pro-natriuretic peptide type-B (NT-proBNP) and the appearance of albuminuria can help detecting organ damage when it is still reversible. A strategy for achieving early diagnosis will be presented. Characterization of the amyloid deposits is a central step in the diagnostic process, since AA amyloidosis reactive to chronic inflammation can be also associated with Waldenström macroglobulinemia, though in only 4% of cases, and the possibility of concomitant hereditary or senile amyloidosis cannot be ignored in this elderly population. Although there is substantial overlap in the clinical manifestations, IgM-AL amyloidosis is a distinct clinical entity characterized by higher frequency of pulmonary and lymph node involvement and of neuropathy, both peripheral and autonomic. The standard prognostic staging system based on cardiac biomarkers (NT-proBNP and troponins) can be applied to IgM-AL amyloidosis, but serum albumin is an additional independent prognostic factor: patients in whom NT-proBNP is >650 ng/L and albumin is <35 g/L have a median survival of only 6 months. The concentration of circulating free light chain (FLC) tends to be lower in IgM-AL amyloidosis than in other patients, and in our series almost 50% of patients have a dFLC <50 mg/L making them not evaluable with the current response criteria. However, higher dFLC (>180 mg/L) is predictive of poorer outcome. Patients with IgM-AL amyloidosis are usually treated with regimens developed for non-IgM AL amyloidosis or for Waldenström macroglobulinemia, and efficacy data often derive from small retrospective series. Almost two thirds of patients respond to standard melphalan/dexamethasone, while the response rate to chlorambucil/prednisone is approximately 30%. Higher response rates (70-80%) were reported with purine analogues, autologous stem cell transplant, and bortezomib/rituximab/dexamethasone. In a collaborative study with the Heidelberg group we observed that the combination of bendamustine, prednisone, and rituximab is a promising rescue regimen, with a 56% overall response rate and at least very good partial responses (VGPR) in 27% of cases. All the patients treated frontline responded and this regimen deserves further investigation. In a large European study VGPR or better was associated with an excellent survival. The availability of novel agents and international collaboration have the potential to improve the outcome of patients with IgM-AL amyloidosis in the near future.