Diagnosis and therapy of amyloidosis

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Systemic amyloidoses are characterized by tissue deposition of different unrelated proteins that undergo conformational changes and aggregate in fibrils. In AL amyloidosis the fibrils are formed by a monoclonal immunoglobulin light chain (LC). The process of LC aggregation and tissue deposition causes dysfunction of the organs involved, with fatal outcome if it is not arrested by therapy. Early diagnosis is crucial in order to establish effective treatment before irreversible organ damage has occurred.

The diagnosis of amyloidosis requires the demonstration of amyloid deposits in tissues using Congo red staining or electron microscopy (EM). The availability of alternative, less invasive, sites can spare the biopsy of the organ involved. In a series of 597 consecutive patients with suspected systemic amyloidosis referred to our center, abdominal fat aspirate (AFA) had 82% sensitivity. The biopsy of a minor salivary gland can detect amyloid deposits in 58% of subjects with negative AFA. Once the presence of the deposits has been established, it is vital to reach unequivocal amyloid typing, since treatment is different in different types of amyloidosis, and mistyping can lead to irrecoverable therapeutic mistakes. The clinical presentation rarely allows discriminating different types of amyloidosis (e.g. macroglossia and periorbital purpura, typical of AL amyloidosis, are present in approximately 10% of patients only). Light microscopy immunohistochemistry has a poor diagnostic performance in AL amyloidosis. At our center immuno EM approaches 100% specificity. Protein identification by mass spectrometry is the gold standard for amyloid protein identification, being now feasible on clinical biopsy samples. Hereditary amyloidosis should be ruled out by DNA analysis. In AL amyloidosis the demonstration of the amyloidogenic LC is essential for diagnosis and assessment of response to treatment. The amyloid forming clone is usually small and a combination of high-resolution techniques, including serum and urine immunofixation and the free LC assay, is needed to grant maximum sensitivity. A monoclonal IgM is present in 5-7% of patients with AL amyloidosis and subjects with IgM-AL amyloidosis usually have lower free LC concentrations.

The treatment of AL amyloidosis is aimed at reducing the concentration of the amyloidogenic LC and this translates into organ function improvement and prolonged survival. We reported a significant survival benefit associated with hematologic response also in subjects with IgM-AL amyloidosis. The therapeutic approach derives from other plasma cell dyscrasias, but patients with AL amyloidosis are more susceptible to

treatment toxicity due to organ, particularly heart, dysfunction. Heart involvement is the most important prognostic determinant, and its presence and severity is best assessed by cardiac biomarkers, natriuretic peptides type B (BNP and NT-proBNP) and troponins (cTn). A staging system based on NT-proBNP and cTn guides the therapeutic choice and is further refined by high-sensitivity assays for cTn. The ability of treatment to prolong survival is strictly contingent upon its ability to induce improvement of cardiac dysfunction or at least to prevent its progression, as assessed by cardiac biomarkers.

Early diagnosis and accurate typing, refined patients stratification and novel therapies, conjugating tolerability with rapid efficacy, monitored with cardiac biomarkers are changing the natural history of AL amyloidosis.