Role of Immunoglobulin Light Chains in AL Amyloidosis

Key words: AL amyloidosis, immunoglobulin, free light chain, Bence Jones protein, stem-cell transplantation

Primary or light chain-associated (AL) amyloidosis is one of the plasma cell dyscrasias that is characterized by the deposition of amyloid fibrils in the systemic organs such as heart, liver, kidney, tongue, gastrointestinal tract, skin, and peripheral nerves. These Congoophilic fibrils mostly consist of either the variable domain (V_L) fragment of the monoclonal immunoglobulin (Ig) light chains or the V_L plus adjacent portion of the constant domain (C_L), or less commonly, the intact light chain (Bence Jones protein, BJP). In the 1960s, Osserman et al first recognized that BJPs play a direct role in the pathogenesis of primary amyloidosis (1). Subsequent studies have aimed at elucidating the relationship between the structure and property of amyloidogenic BJPs. Solomon et al demonstrated the development of amyloid deposits in mice by injection with BJPs obtained from patients with AL amyloidosis, and described the importance of certain amino acid sequences of BJPs for amyloidogenicity (2). The immunochemical and molecular analysis of Ig light chains revealed that amyloid property and organ specificity are associated with particular types of V_L subgroups (3, 4).

Monoclonal Igs serve as important clinical markers for monitoring plasma cell dyscrasias. Unfortunately, these products are generally undetectable in serum or urine of AL amyloidosis patients by conventional electrophoresis techniques. Several attempts were made to establish an assay system for intact light chains, but none of these assays were used for laboratory examinations in the clinical setting because of a lack of specificity and complexity of the methods. Recently, a high-sensitive nephelometric assay for Ig light chains has been developed using latex-conjugated antibodies specific for the epitopes of free light chains but not heavy chains (5). This assay system is now available as a diagnostic kit (Freelite™, The Binding Site Ltd, Birmingham, UK).

In this issue of Internal Medicine, Matsuda and colleagues report the usefulness of this serum free light-chain assay before and after treatment in 25 Japanese patients with AL amyloidosis (6).

They have confirmed and extended previous results indicating that this assay contributes to the diagnosis and monitoring of patients with AL amyloidosis (7–9). In fact, serum free light chains have a favorable characteristic of a short half-life for rapid assessment, but these levels are significantly affected by the glomerular filtration rate especially in patients with renal failure. Alternatively, they employed a kappa/lambda ratio of the free light chains, and revealed a potential benefit of the ratio for evaluating the response, monitoring the disease, or ultimately, for predicting the prognosis after therapy.

Treatment of AL amyloidosis has been directed toward reducing the synthesis of the amyloid precursors from plasma cells through conventional or high-dose chemotherapy. High-dose melphalan with autologous stem-cell transplantation has extended the overall survival in selected patients; however, the prognosis remains extremely poor due to the persistence of the amyloid deposits and/or organ dysfunction in most patients (10). Current studies focus on further understanding the molecular mechanism of amyloid formation and resorption, and providing new insight into the development of novel molecular-targeted therapies (11). For example, administration of monoclonal antibodies that recognize an epitope common to the beta-pleated structure of amyloid has been shown to induce marked reduction of amyloid burden *in vivo* model (12). In future clinical studies, this free light-chain assay will be extensively applied to the patients with plasma cell dyscrasias including multiple myeloma and AL amyloidosis.

Shuji OZAKI, MD

Division of Transfusion Medicine, Tokushima University Hospital,
2-50 Kuramoto-cho, Tokushima 770-8503

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