Diagnosis and Management of Immunoglobulin Light Chain Amyloidosis

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**INTRODUCTION**

The term *amyloidosis* refers to a fascinating group of disorders that share a common pathogenesis of extracellular deposition of amyloid material. Fundamentally, it is a disorder of the secondary structure of select proteins whereby the amyloidogenic proteins are misfolded into a β-pleated sheet configuration, resulting in the formation of insoluble extracellular amyloid fibrils. The amyloid fibrils appear as amorphous eosinophilic material when hematoxylin and eosin–stained tissue is examined under light microscope. Electron microscopy reveals remarkable similarity between the amyloid fibrils derived from different precursor proteins in that they range from 7.5 to 10 nm in diameter. This ultrastructural similarity is the underlying basis for the characteristic red-green birefringence with Congo red staining observed under polarized microscopy, the pathological hallmark of the disease.

Despite the profound similarity in the biochemical composition of the amyloid, it is the nature and source of the precursor (amyloidogenic) protein that separate this homogeneous pathological entity into very distinct clinical disorders belonging to inflammatory, hereditary, infectious, degenerative, and neoplastic categories. More than 25 precursor proteins have been identified whose structural variation can render them amyloidogenic and result in various diseases ranging from Alzheimer’s dementia to familial amyloid polyneuropathy, prion disease, senile amyloid cardiomyopathy, and primary systemic amyloidosis. Several schemas have been used for clinical classification of these disorders. The conventional classification of amyloidosis divides the disease into systemic and localized forms. Systemic amyloidosis is further divided into primary, secondary, and familial (hereditary) types. This review focuses on the diagnosis and management of primary systemic amyloidosis.

Primary systemic amyloidosis is a fatal clonal plasma cell dyscrasia characterized by aberrant production of amyloidogenic immunoglobulin or its components. In the most common form of primary systemic amyloidosis (>90% of cases), immunoglobulin light chain (AL) is the precursor protein; hence, the disorder is referred to as AL amyloidosis.

**ETIOLOGY AND EPIDEMIOLOGY**

AL amyloidosis is a rare disease; each year nearly 3000 new cases are diagnosed in the United States, which translates into 9 cases per million persons. The exact etiology of AL amyloidosis remains unknown. The predominance of lambda light chain as the pathogenic light chain (kappa-to-lambda ratio of 1:3) and the use of a restricted repertoire of light chain variable region gene segments during the immunoglobulin gene recombination process by AL plasma cells are suggestive of a clonal selection process triggered by an as yet unidentified antigen. Interestingly, this restricted recombination is also hypothesized to impart relative organ tropism of the amyloidogenic light chain; for example, patients with clones from the 6a variable λ VI germline gene segment are more likely to present with renal involvement. Most cases of AL amyloidosis present as de novo disease; a small fraction of cases evolve from preexisting multiple myeloma or, rarely, from other immunosecretory malignancies such as Waldenstrom’s macroglobulinemia.

**CLINICAL FEATURES AND PRESENTATION**

The clinical manifestations of AL amyloidosis result from organ dysfunction. The underlying basis for organ dysfunction is not completely understood, but pressure atrophy of the parenchymal tissue and direct cellular cytotoxicity are considered to be the major pathogenic mechanisms. AL amyloidosis can affect virtually any organ, but most commonly it affects kidney, peripheral nerves, heart, gastrointestinal tract, liver, and soft tissues. Frequently, more than one organ is involved, and the number of involved organs has been associ-