

cells produce an LC that misfolds and leads to AL amyloidosis or an LC that folds properly, allowing the cells to inexorably expand over time and develop into multiple myeloma (Chap. 136), may depend upon primary sequence or other genetic or epigenetic factors. AL amyloidosis can occur with multiple myeloma or other B lymphoproliferative diseases, including non-Hodgkin's lymphoma (Chap. 134) and Waldenström's macroglobulinemia (Chap. 136). AL amyloidosis is the most common type of systemic amyloidosis diagnosed in North America. Its incidence has been estimated at 4.5 cases/100,000 population; however, ascertainment continues to be inadequate, and the true incidence may be much higher. AL amyloidosis, like other plasma cell diseases, usually occurs after age 40 and is often rapidly progressive and fatal if untreated.

Pathology and Clinical Features Amyloid deposits are usually widespread in AL amyloidosis and can be present in the interstitium of any organ outside the central nervous system. The amyloid fibril deposits are composed of full-length 23-kDa monoclonal immunoglobulin LCs as well as fragments. Accessory molecules co-deposited with LC fibrils (as well as with other amyloid fibrils) include serum amyloid P component, other proteins, glycosaminoglycans, and metal ions. Although all kappa and lambda LC subtypes have been identified in AL amyloid fibrils, lambda subtypes predominate. The lambda 6 subtype appears to have unique structural properties that predispose it to fibril formation, often in the kidney.

AL amyloidosis is often a rapidly progressive disease that presents as a pleiotropic set of clinical syndromes, recognition of which is key for initiation of the appropriate workup. Nonspecific symptoms of fatigue and weight loss are common; however, the diagnosis is rarely considered until symptoms referable to a specific organ develop. The kidneys are the most frequently involved organ and are affected in 70–80% of patients. Renal amyloidosis usually manifests as proteinuria, often in the nephrotic range and associated with hypoalbuminemia, secondary hypercholesterolemia and hypertriglyceridemia, and edema or anasarca. In some patients, interstitial rather than glomerular amyloid deposition can produce azotemia without proteinuria. The heart is the second most commonly affected organ (50–60% of patients), and cardiac involvement is the leading cause of death from AL amyloidosis. Early on, the electrocardiogram may show low voltage in the limb leads with a pseudo-infarct pattern. Echocardiographic features of disease include concentrically thickened ventricles and diastolic dysfunction with an abnormal strain pattern a “sparkly” appearance has been described but is often not seen with modern high-resolution echocardiographic techniques. Poor atrial contractility occurs even in sinus rhythm, and patients with cardiac amyloidosis are at risk for development of atrial thrombi and stroke. Cardiac MRI can show increased wall thickness, and characteristic enhancement of the sub-endocardium has been described following injection of gadolinium contrast. Nervous system symptoms include peripheral sensorimotor neuropathy and/or autonomic dysfunction manifesting as gastrointestinal motility disturbances (early satiety, diarrhea, constipation), impotence, orthostatic hypotension, and/or neurogenic bladder. Macroglossia (Fig. 137-2A), a pathognomonic sign of AL amyloidosis, is seen in only ~10% of patients. Liver involvement causes cholestasis

and hepatomegaly. The spleen is frequently involved, and there may be functional hyposplenism in the absence of significant splenomegaly. Many patients experience “easy bruising” due to amyloid deposits in capillaries or deficiency of clotting factor X, which can bind to amyloid fibrils; cutaneous ecchymoses appear, particularly around the eyes, producing the “raccoon-eye” sign (Fig. 137-2B), another uncommon but pathognomonic finding. Other findings include nail dystrophy (Fig. 137-2C), alopecia, and amyloid arthropathy with thickening of synovial membranes in the wrists and shoulders. The presence of a multisystemic illness or general fatigue along with any of these clinical syndromes should prompt a workup for amyloidosis.

Diagnosis Identification of an underlying clonal plasma cell or B lymphoproliferative process and a clonal LC are key to the diagnosis of AL amyloidosis. Serum protein electrophoresis and urine protein electrophoresis, although of value in multiple myeloma, are *not* useful screening tests if AL amyloidosis is suspected because the clonal LC or whole immunoglobulin often is not present in sufficient amounts to produce a monoclonal “M-spike” in the serum or LC (Bence Jones) protein in the urine. However, more than 90% of patients with AL amyloidosis have serum or urine monoclonal LC or whole immunoglobulin detectable by immunofixation electrophoresis of serum (SIFE) or urine (UIFE) (Fig. 137-3A) or by nephelometric measurement of “free” LCs (i.e., LCs circulating in monomeric form rather than in an immunoglobulin tetramer with heavy chain). Examining the ratio as well as the absolute amount of free LCs is essential, as renal insufficiency reduces LC clearance, elevating both isotypes. In addition, an increased percentage of plasma cells in the bone marrow—typically 5–30% of nucleated cells—is found in ~90% of patients. Kappa or lambda clonality should be demonstrated by flow cytometry, immunohistochemistry, or in situ hybridization for LC mRNA (Fig. 137-3B).

A monoclonal serum protein by itself is not diagnostic of amyloidosis, since monoclonal gammopathy of uncertain significance is common in older patients (Chap. 136). However, when monoclonal gammopathy of uncertain significance is found in patients with biopsy-proven amyloidosis, the AL type should be strongly suspected. Similarly, patients thought to have “smoldering myeloma” because of a modest elevation of bone-marrow plasma cells should be screened for AL amyloidosis if they have signs or symptoms of renal, cardiac, or neurologic disease. Accurate tissue amyloid typing is essential for appropriate treatment. Immunohistochemical staining of the amyloid deposits is useful if they bind one LC antibody in preference to the other; some AL deposits bind antibodies nonspecifically. Immunoelectron microscopy is more reliable, and mass spectrometry-based microsequencing of small amounts of protein extracted from fibril deposits can also be undertaken. In ambiguous cases, other forms of amyloidosis should be thoroughly excluded with appropriate genetic and other testing.

TREATMENT AL AMYLOIDOSIS

Extensive multisystemic involvement typifies AL amyloidosis, and the median survival period without treatment is usually only ~1–2 years from the time of diagnosis. Current therapies target the



FIGURE 137-2 Clinical signs of AL amyloidosis. **A.** Macroglossia. **B.** Periorbital ecchymoses. **C.** Fingernail dystrophy.