AL Amyloidosis: Who, What, When, Why, and Where

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In the current issue of ONCOLOGY, Gertz and Dispenzieri provide a scholarly review of the early recognition, diagnosis, and treatment of immunoglobulin light-chain (AL) amyloidosis.

Since the first reports of amyloid being “cellulose” (reported by Virchow in the mid-1850s) and the identification of amyloid fibril ultrastructure in the late 1950s, amyloidosis has remained an enigmatic disease. However, progress in our ability to diagnose and treat amyloidosis has advanced tremendously in recent years. The use of chemotherapy and immunomodulatory agents has changed AL amyloidosis from a uniformly fatal disease to one from which many patients can achieve hematologic remissions, accompanied by improvement in organ function, quality of life, and survival. Progress is now being made in other forms of amyloidosis as well, with promising small-molecule therapeutics undergoing clinical trials. Because of the availability of effective treatments, clinicians now more than ever need to be aware of the clinical manifestations of the disease, the approach to diagnosis, and the options for treatment that have dramatically improved outcomes for some patients.

Potentially effective and life-saving treatment of patients with systemic amyloidosis is dependent on: (1) an early recognition of a clinical syndrome suspicious for amyloidosis; (2) tissue diagnosis of amyloidosis; (3) accurate typing of amyloid fibrils; and (4) initiation of appropriate therapy, if available for the type diagnosed.

A critical theme of this review and the two cases it presents is that amyloidosis can masquerade as more common diseases associated with cardiomyopathy (case 1) or nephrotic syndrome (case 2). In fact, amyloidosis, not syphilis, is “the great mimic” of the 21st century. In addition to cardiomyopathy and nephropathy, amyloidosis should be considered in patients presenting with symptoms and signs as diverse as unexplained autonomic neuropathy with postural hypotension or gastrointestinal (GI) dysmotility, peripheral neuropathy in the absence of diabetes or heavy alcohol use, GI symptoms with friable GI mucosa or bleeding, calcific lymphadenopathy, skin thickening or non-malignant breast nodules, as well as the pathognomonic signs of macroglossia and periorbital ecchymosis. In any of these clinical settings, and particularly in patients with combinations of symptoms of systemic disease, the diagnosis of amyloidosis should be excluded or established through Congo red staining of an involved organ biopsy specimen or surrogate abdominal fat aspirate.

Amyloidosis due to clonal immunoglobulin light chains, or AL amyloidosis, is the type that comes to the attention of the practicing hematologist-oncologist. In addition to the association with a subtle clonal plasma cell disorder or overt multiple myeloma as discussed in the Gertz and Dispenzieri review, the hematologist-oncologist should be aware that other clonal lymphoid processes may produce amyloidogenic light chains that can cause disease. Associations of amyloidosis with lymphoplasmacytic lymphoma, marginal zone lymphoma, and chronic lymphocytic leukemia have been reported. [1] Amyloidosis associated with these lymphoproliferative diseases is still considered to be “primary,” or “AL” type, not secondary.

Gertz and Dispenzieri describe the process of diagnosis and treatment of AL. We would also emphasize the importance of conscientious consideration of the differential diagnosis before committing a patient to potentially toxic chemotherapy. AL amyloidosis is only one of the major forms of systemic amyloidosis, and there is considerable clinical overlap with the other types. Amyloid cardiomyopathy with wall thickening, diastolic dysfunction, and arrhythmia can occur in familial amyloidosis (AF), due to mutant forms of transthyretin (TTR), and also in so-called senile systemic amyloidosis (SSA), due to wild-type TTR. Neuropathy also occurs with some forms of mutant TTR-associated amyloidosis (ATTR)—as familial amyloidotic polyneuropathy that is endemic in some areas of Portugal, Japan, and Sweden, but found worldwide. Neuropathy is a manifestation of some of the rare AF disorders, including amyloidosis due to mutations of lysozyme, fibrinogen, and apolipoprotein AII, for example. Older patients with SSA or AF frequently have a monoclonal
gammopathy of unknown significance (MGUS), and African Americans born with the common amyloidogenic V122I mutant of TTR can develop AL amyloidosis.[2] The unequivocal identification of the protein forming the amyloid fibril is essential for the choice of therapy. A mistake in protein typing may have catastrophic therapeutic consequences,[3,4] such as the administration of cytotoxic chemotherapy in a patient with ATTR amyloidosis who should receive a liver transplant. Recent advances in immunoelectron microscopy[5] and proteomics techniques have significantly improved the typing of amyloid deposits.[6,7]

Treatment of AL amyloidosis has been well reviewed in this paper; the authors have included discussion of novel therapies and available clinical trials, as well as mention of preclinical immunotherapy, animal model systems for new anti-fibril therapies, and siRNA therapeutics.[8] Dispenzieri and Gertz highlight the remarkable benefits of high-dose melphalan and autologous stem-cell transplantation (HDM/SCT). We have treated more than 500 patients with this approach, and like the Mayo Clinic, we have achieved a high rate of hematologic and organ response with manageable morbidity and mortality of ~5% in recent years.[9] However, the reader may be aware that the single randomized study comparing HDM/SCT to oral melphalan and dexamethasone failed to show a benefit for dose-intensive therapy.[10] With 29 centers across France participating, early mortality was 38%, including 4 deaths during stem-cell mobilization and 9 early deaths after SCT. That study highlighted the need for careful patient selection and institutional experience in the peri-transplant management of these challenging patients. Treatment of AL amyloidosis is an example of highly personalized medicine, as each patient has a different constellation of organ involvement and prognostic factors, ranging from nutritional state and performance status to cardiac biomarkers and functional reserve. Treatment decisions should involve a multidisciplinary patient assessment[11] at centers specializing in treatment and research on amyloidosis where state-of-the-art clinical trials are available.

In conclusion, and in full agreement with Gertz and Dispenzieri, in amyloidosis it is critical to identify WHO has the disease and WHAT type of systemic amyloidosis it is; WHEN alludes to the need for early diagnosis before irreversible organ damage has occurred; WHY, because effective treatment is now available; and finally, patients with rare diseases may benefit from referral to specialized centers of excellence WHERE sophisticated diagnostic techniques and a repertoire of clinical trials and protocols are available to match patients with suitable studies.

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**References:**

**REFERENCES**


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