Diagnosis and Treatment of AL and ATTR Amyloidosis

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Presenters' disclosures of conflicts of interest are found at the end of this article.

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Abstract

At JADPRO Live Virtual 2020, Beth Faiman, PhD, RN, MSN, APRN-BC, AOCN®, FAAN, and Tiffany Richards, PhD, ANP-BC, AOCNP®, differentiated between AL and ATTR amyloidosis, discussed key considerations in selecting therapy, and identified ways that advanced practitioners can manage the supportive care needs of this patient population.

Vast improvements in the diagnosis and management of amyloidosis have underscored the importance of prompt diagnosis and effective treatment. During JADPRO Live Virtual 2020, Beth Faiman, PhD, RN, MSN, APRN-BC, AOCN®, FAAN, of Cleveland Clinic Taussig Cancer Institute, and Tiffany Richards, PhD, ANP-BC, AOCNP®, of The University of Texas MD Anderson Cancer Center, discussed the differences between immunoglobulin light chain (AL) and transthyretin (ATTR) amyloidosis and listed key considerations when selecting appropriate therapy. Drs. Faiman and Richards also identified ways that advanced practitioners can successfully manage the supportive care needs of patients with AL and ATTR amyloidosis.

AL AND ATTR AMYLOIDOSIS

Amyloidosis is a multisystemic disorder that can affect the heart, kidneys, nerves, liver, lungs, and gastrointestinal tract of patients afflicted with the disease. Although there are at least 14 proteins—and possibley others—that transform into systemic amyloidosis, Drs. Faiman and Richards focused on the two most common types: AL and ATTR amyloidosis.

AL amyloidosis is characterized by a clonal population of bone marrow plasma cells that produces a monoclonal light chain of kappa (κ) or lambda (λ) type as either an intact molecule or a fragment. AL can occur with any B-cell–secreting neoplasm, such as Waldenström macroglobulinemia, chronic lymphocytic leukemia (CLL), and multiple myeloma. The inability to degrade these misfolded proteins leads to deposit in various organs and the problematic diagnosis of amyloidosis.

Although amyloidosis is quite rare, said Dr. Faiman, ATTR amyloidosis has been found in as many as 25% of patients older than 85 years

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of age on autopsy. However, AL amyloidosis is more commonly seen by advanced practitioners in oncology than the ATTR type.

ATTR amyloidosis can be inherited (caused by a faulty, mutated gene) or wild-type (developed with age). There are over 120 different mutations in the *TTR* gene, but the most common ATTR mutations are the ATTR T60A variant, ATTR V30M variant, and ATTR V122I variant.

DIAGNOSING PLASMA CELL DISORDERS

When working up a patient with a possible diagnosis of amyloidosis, Dr. Faiman underscored the importance of identifying lambda free light chains.

"There may only be a lambda light chain of 144, which is very low for a diagnosis of multiple myeloma, but the clonal light chain may be high enough of a burden to aggregate into a beta-sheet of fibrils, and lead to heart, nerve, or kidney damage," she said.

While patients with smoldering myeloma will have a higher percentage of bone marrow plasma cells, active multiple myeloma occurs with higher free light chains, high clonal bone marrow plasma cell percentage, and evidence of end-organ damage.

"The key is to look for organ damage related to the abnormal paraprotein," Dr. Faiman continued. "Find out where the abnormal band is located, and then rule out multiple myeloma, monoclonal gammopathy of undetermined significance, and Waldenström macroglobulinemia."

Table 1. Diagnostic Workup for Monoclonal Gammopathies

Lab tests
- Serum protein electrophoresis (SPEP)
- Urine protein electrophoresis (UPEP)
- CBC + differential + chemistry including albumin and β_2 microglobulin and LDH
- FLC ratio of free kappa/lambda light chains (plasma)
- Monoclonal protein analysis (MPA)

Bone marrow biopsy
- FISH, cytogenetics, +/- gene expression profiling (GEP)

Imaging
- Skeletal survey, MRI, CT, PET scan

Note. The key is to look for organ damage related to the abnormal paraprotein. Where is the abnormal band located? Rule out MM, MGUS, WM, etc. Information from Faiman (2014); Ghobrial et al. (2014); Rajkumar et al. (2014).

The diagnostic workup for monoclonal gammopathies involves a "cornucopia of tests." (Table 1)

Dr. Faiman also noted that it's important to keep in mind that a diagnosis of AL amyloidosis should be suspected in any patient with nondiabetic nephrotic syndrome or nonischemic cardiomyopathy with "hypertrophy" on echocardiography. In addition, patients should be tested for dysparaproteinemia if they have anemia, proteinuria, hypercalcemia, or progressive renal dysfunction.

"Amyloidoses are difficult to diagnose and are often underdiagnosed," she said.

SYMPTOMS OF ATTR AND AL AMYLOIDOSIS

Although kidney involvement is generally not present in ATTR, Dr. Richards noted that symptoms of ATTR and AL amyloidosis share similarities and can present in a variety of organ systems. Patients with kidney involvement may complain of "foamy" urine due to the presence of protein in the urine, and albuminuria is usually greater than 70%.

"Of note, there may not be a monoclonal protein in the urine," said Dr. Richards. "Anybody with nephrotic proteinuria should undergo a light chain assay.'"

With skin involvement, patients may develop easy bruising or bleeding or tongue enlargement that can lead to macroglossia.

Neurologic symptoms include numbness and tingling, pain in fingers and toes, and/or problems with movement such as carpel tunnel syndrome as the disease progresses. Patients may also develop autonomic neuropathy that includes orthostatic hypotension, impotence, and gut problems such as diarrhea, constipation and early satiety.

Other symptoms include periorbital purpura or bruising of the skin around the eyes. Although less than 15% of patients with AL amyloidosis experience this problem, it is hardly ever caused by anything else. With ATTR amyloidosis, patients may also experience vision changes.

Finally, cardiac involvement may lead to shortness of breath, peripheral edema, exertional dyspnea, fatigue, heart block, or conduction system disorders. However, patients with cardiomyopathy may not present with any symptoms.

"In about one third of patients, the disease is manifested by cardiac events," said Dr. Richards,

who noted that the most common electrocardiogram (EKG) abnormality in cardiac amyloidosis is low voltage in the limb leads (50%).

The echocardiogram may show left ventricular hypertrophy with evidence of diastolic dysfunction and "sparkling" appearance of the myocardium, and septal thickness can be seen in more advanced disease.

"We also need to check for global strain, and if we suspect amyloidosis involving the heart. The lower the number, the more strain is present. We should obtain a cardiac MRI and look for late enhancement of the myocardium," said Dr. Richards. "We often have to obtain an endomyocardial biopsy to get a definitive diagnosis. Unfortunately, in patients who have late-stage amyloidosis with cardiomyopathy, overall survival is only 6 to 9 months."

TREATMENT OF AMYLOIDOSIS

Most drugs used to treat multiple myeloma can be used to treat amyloidosis, especially AL amyloidosis, said Dr. Faiman, who noted that targeting the clonal plasma cell population with a plasma cell-directed therapy is the current standard of care of treatment.

Patients with amyloidosis tend to be treated outside the context of a clinical trial for a fixed duration of time in most settings. Those with less than 10% plasma cells typically receive melphalan (200 mg/m^2) followed by an autologous stem cell transplant. Patients who achieve a hematologic very good partial remission can be observed off therapy.

"For transplant-eligible patients with AL amyloidosis, it's important to distinguish the number of clonal bone marrow plasma cells because that's going to drive your decision-making," she continued. "If the individual has a bone marrow plasma cell percentage greater than 10%, multiple myeloma symptoms, or high-risk cytogenetics, then we treat them like a multiple myeloma patient."

The multiple myeloma paradigm is induction therapy of cyclophosphamide, bortezomib, and dexamethasone outside of a clinical trial. If that patient achieves a hematologic very good partial remission, the provider can consider maintenance with a bortezomib-based therapy in many centers.

"Treatment varies depending on the center, but the goal is to prevent further organ damage," said Dr. Faiman. "Until recently, there were no FDA-approved drugs to treat AL amyloidosis."

Cyclophosphamide, bortezomib, and dexamethasone (CyBorD) is the gold standard of care in patients with newly diagnosed AL amyloidosis. The ANDROMEDA study evaluated the safety and efficacy of daratumumab hyaluronidase (FASPRO) +/- CyBorD (Palladini et al., 2020). In patients with newly diagnosed AL amyloidosis who received DARA+CyBorD, a 96% overall response rate (36% complete response) was observed (Palladini et al., 2020).

"That's an excellent hematologic response in this group of patients, and there were organ responses too," said Dr. Faiman. "Over three quarters of patients had a response in their renal disease, and half of patients with cardiac and liver involvement responded to this combination."

Finally, more than 50% of patients with AL amyloidosis have immunoglobulin heavy chain translocation (11;14). Venetoclax (Venclexta), a BCL2 inhibitor, is currently being investigated in this patient population. Hematologic response rates have been seen in more than two thirds of patients, and more than one third of patients have had an organ response.

"These are also excellent responses for a relapsed/refractory patient population," said Dr. Faiman. ●

Disclosure

Dr. Faiman has acted as a consultant for Celgene, GlaxoSmithKline, and Takeda, and has served on advisory boards for Takeda. Dr. Richards has acted as a consultant for Celgene, GlaxoSmithKline, Janssen, and Takeda.

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