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AL Amyloidosis and Multiple Myeloma: Early Detection and Treatment

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Abstract

Light chain (AL) amyloidosis is a rare but serious plasma cell disorder in which misfolded light-chain proteins form amyloid fibrils that deposit in organs—most commonly the heart and kidneys—leading to progressive dysfunction. Early diagnosis and treatment are critical, as delayed recognition often results in irreversible organ damage.

Keywords: AL Amyloidosis; Multiple Myeloma; Light Chains; Plasma Cell; T(11,14)

Abbreviations: AL: Light Chain; MM: Multiple Myeloma; VEN: Venetoclax; BOR: Bortezomib; DARA: Daratumumab; VEN: Venetoclax; Ben: Bendamustine; WHO: World Health Organization; PCN: Plasma Cell Neoplasms

Introduction

Light chain (AL) amyloidosis is a rare disease that occurs when a plasma cell proliferative disorder produces monoclonal light chains, which misfold and deposit as fibrils in organs and tissues [1]. Both AL amyloidosis and multiple myeloma (MM) diseases can be shown in the same patient at the same time or at different times. Three scenarios can be anticipated: A. diagnosis of AL followed by development of MM in the future as a second primary malignancy is very infrequent.

B. diagnosis of MM and appearance of AL later as a second primary malignancy is very rare. C. diagnosis of AL and MM synchronously is relatively common in daily clinical practice. Probably, the most appropriate period to define synchronous cancer is 4 months after the diagnosis of the first cancer. Keep in mind the difficulty to carry out an efficient diagnostic workup in sometimes complex clinical backgrounds and the available evidence comes largely from clinical case reports and some real-world series with heterogeneous results [2].

AL amyloidosis and MM share a common causal root, namely, the presence of clonal malignant plasma cells in the bone marrow [3]. The fifth edition of the World Health Organization (WHO) classification of lymphoid tumors (WHO-HAEM5) classifies systemic AL amyloidosis and MM within the category of "Plasma cell neoplasms" (PCN) and other diseases with paraproteins". AL amyloidosis is included in the family of "Diseases with monoclonal Ig deposition" whereas MM is incorporated into the family of "PCNs" [3]. Plasma cells from patients with AL amyloidosis most closely resemble secondary lymphoid organ plasma cells (SLO-PCs), whereas MM cells are closer to peripheral blood plasma cells (PB-PCs) and newborn bone marrow plasma cells (BM-PCs).

The different behavior of these cells in the two diseases, leads to profoundly different clinical consequences. In the case of MM, clonal plasma cells accumulate in the bone marrow, leading to anemia and bone destruction, among other harmful effects. In the AL amyloidosis, the clonal plasma cells do not accumulate but induce the deposition of light chains in various organs as amyloid fibrils. The deposition of amyloid fibrils is independent of the tumor burden [3]. The amyloid proteins that are circulating and not yet deposited in the organs are also toxic. In the case of AL amyloidosis, serum free light chain levels are closely correlated with the degree of disease [4].

Presentation and Organ Involvement [5]

The most common symptom of AL amyloidosis is fatigue. It is reported by 80% of patients. Other common symptoms include exertional dyspnea, peripheral edema, paresthesias, weight loss,

purpura, dysgeusia, xerostomia, and macroglossia. The 2 most involved organs are the heart and the kidneys; each exists in 60% to 80% of patients.

Heart involvement is defined based on

- Typical echocardiographic findings are thickened heart walls, restrictive filling pattern, sparkling appearance of the myocardium, and abnormal strain pattern with a base-to apex gradient.
- Cardiac magnetic resonance shows late gadolinium enhancement, when echocardiographic findings are equivocal.
- Elevated soluble cardiac biomarkers, cardiac troponins and natriuretic peptides, are sensitive but not specific.
- Endomyocardial biopsy should be mainly used when heart involvement is highly suspected but tissue diagnosis from more accessible tissues is not successful.

Renal involvement is defined on the basis of

- The presence of more than 0.5 g/24-hour nonselective proteinuria.
- More than half of the patients with renal AL amyloidosis present with nephrotic-range proteinuria.
- Kidney involvement can be manifested with or without renal failure.
- Rarely, renal failure without proteinuria is seen in vascular-limited renal involvement.

Other organ involvement is peripheral neuropathy, autonomic neuropathy, liver (hepatomegaly or elevated serum alkaline phosphatase, jaundice, weight loss), gastrointestinal tract (diarrhea, constipation, malabsorption, weight loss, gastrointestinal bleeding), muscle (muscle weakness, myalgia, pseudohypertrophy, atrophy), joints (polyarthropathy), spleen (hyposplenism), lungs (dyspnea, cough, diffuse interstitial infiltrates on imaging), bleeding diathesis (deficiencies of clotting factors, such as factor X), and skin (alopecia, purpura). Vascular involvement can result in exercise-induced limb claudication or angina pectoris as well as in jaw claudication on chewing.

Diagnosis Of AL Amyloidosis

The minimal evaluation should include measurement of seated and standing blood pressure, N-terminal brain natriuretic peptide (NT-proBNP) or brain natriuretic peptide, troponin T or troponin I, alkaline phosphatase, creatinine, and 24-hour urine protein. Nerve conduction studies and electromyography aid in assessment of large-fiber peripheral neuropathy. Autonomic testing is appropriate based on symptoms and should include evaluation of sweating and cardiovagal and adrenergic function as well as of gastric motility and bladder emptying [5].

The diagnosis of amyloidosis relies on demonstration of amyloid deposits on a tissue sample of the affected organ. However, a more accessible tissue, such as subcutaneous fat, should initially be pursued when suspicion for amyloidosis is raised. Fat aspiration combined with bone marrow biopsy (performed for assessment of the underlying plasma cell disorder) will yield the diagnosis in approximately 90% of patients [5]. Survival is predicted by the organ affected as well as the depth and speed of hematologic response, which are necessary for organ function to be restored [4]. The degree of hematological response is evaluated by the decrease in sFLC [6].

Treatment options for AL amyloidosis

Most treatment options for AL amyloidosis aimed at decreasing the serum levels of light chains with the use of chemotherapy aimed at suppressing the underlying secreting plasma cell clone [4]. Autologous stem cell transplant (ASCT) has been associated with rapid and durable suppression of the plasma cell clone and therefore, has been a commonly used therapeutic option in AL amyloidosis [4]. Steroids, alkylating agents, and proteasome inhibitors (PIs) have emerged as the first-line combination drug therapy in patients with AL amyloidosis, with the most common regimen being CyBorD. Anti CD38 monoclonal antibodies (mAb), such as daratumumab (DARA) have demonstrated improved outcomes when combined with CyBorD with a low side effect profile [7].

DARA received approval in combination with CyBorD in frontline setting. Unfortunately, some patients will still not achieve complete response (CR) or ultimately relapse [6]. IMiDs are less favorable as first-line therapy but should be considered strongly in cases of refractory/relapsed disease or for maintenance therapy in AL amyloidosis [7]. Venetoclax (VEN) is an oral BCL-2-selective BH3 mimetic. MM cell lines with t(11;14) and MM patients shows response to VEN. This is partly attributed to greater co-dependence of t(11;14) clones on BCL-2. VEN is safe [6]. t(11;14) is more commonly present in AL (60%) than in MM (20%) patients [3].

VEN alone or in combination with bortezomib (BOR) and/or DARA cause rapid and deep organ and hematological responses in AL amyloidosis [6]. VEN combined with dexamethasone alone or with other plasma-cell directed therapies shows significant efficacy in relapsed-refractory AL amyloidosis with t(11;14). Over 80% of patients achieved very good partial response (VGPR) after 2 cycles of VBT therapy. This approach is particularly critical for dara-refractory patients where therapeutic options are extremely limited. A clinical trial investigating the role of VEN in relapsed-refractory AL amyloidosis is ongoing [8].

Bendamustine (Ben) Therapy

Bendamustine is a chemotherapeutic agent that has properties of both alkylators and antimetabolite. Bendamustine

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and prednisolone showed a better hematological response in IgM-AL amyloidosis patients compared to non-IgM-AL refractory/relapsed amyloidosis. The overall hematological response was 35% and the median PFS was 9 months. Patients with progressive or persistent AL amyloidosis received one or more therapy achieved a PR of 57% or better, and median PFS of 11.3 months and median OS of 18.2 months on bendamustine and dexamethasone (Ben-D) combination in phase II trial. Grade 3-4 toxicities developed in two-thirds of patients, with myelosuppression and fatigue being the most common.

More research on the effect of bendamustine in refractory/relapsed AL amyloidosis is needed to investigate its role [7]. The burden of symptoms often depends on the burden of amyloid organs deposition. Two monoclonal antibodies (NEOD001 and CAEL-101) that target the products of the misfolded light chain are under trial. NEOD001 (now called birtamimab) targets a specific epitope present on abnormally folded light chains only. It can bind and neutralize them by facilitating their absorption and clearance. Its benefit was suggested in subgroup analysis of VITAL in Mayo Stage IV patients having severe cardiac involvement.

CAEL-101 is a byproduct of monoclonal plasma cell malignant expansion. It has a strong affinity to kappa and lambda light chains. By binding to kappa and lambda light chains, it initiates neutrophil mediated phagocytosis and clearance of these light chains. This may decrease the light burden in organs and improve overall organ response to AL amyloidosis treatment. It showed an objective cardiac and renal response in 67% of the patients in phase I a/b clinical trial. No adverse events grade 4/5 was reported [7].

Conclusion

Treatment of AL amyloidosis is mainly based on experiences with MM treatment. Research focused on a better understanding of the pathology of AL amyloidosis. Targeted clinical trials on amyloid Component are ongoing.

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