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CLINICAL VIGNETTE

Systemic Light-Chain Amyloidosis Presenting with Hypercalcemia and Found Incidentally after Thyroid Surgery

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Background

Systemic amyloidosis is a rare infiltrative disorder that involves misfolded protein deposition throughout the body, classically presenting with symptoms like fatigue, generalized edema, and shortness of breath. It is commonly treated with chemotherapy or autologous stem cell transplant; however, new therapies are on the horizon that targets the amyloid deposits.

We present a case in which systemic amyloidosis was diagnosed after the surgical removal of the parathyroid glands for symptomatic hypercalcemia. Within a few months of diagnosis, the patient developed acute decompensated heart failure that was consistent with cardiac amyloidosis. The bone marrow was subsequently confirmed to be involved as well. Subsequently, the patient was enrolled in a randomized clinical trial involving a novel drug that targets amyloid deposits.

Case presentation

A 74-year-old Caucasian woman presented to the endocrine department for evaluation of hypercalcemia. Her only reported symptoms were worsening fatigue, lower extremity swelling and dyspnea on exertion of three months' duration. She had a past medical history of paroxysmal atrial fibrillation and bilateral breast cancer. She had normal cardiac function on echocardiogram four months before presentation, and she was on metoprolol and anticoagulation for her atrial fibrillation. Her breast cancer was diagnosed twenty years prior with bilateral multifocal invasive ductal carcinoma for which she underwent bilateral mastectomies.

The initial workup revealed calcium levels ranging from 10-11 mg/dl, and mildly elevated PTH (74 pg/ml, normal range 14-72 pg/ml). Vitamin D levels, UPEP/SPEP, and mammogram were normal. SPECT CT Sestamibi scan revealed a likely parathyroid adenoma. Thyroid ultrasound showed three thyroid nodules and one parathyroid adenoma with increased vascularity in bilateral lobes. She ultimately underwent a parathyroidectomy and a left thyroidectomy to re-sect the larger of the three thyroid nodules. Biopsy results showed a fully encapsulated papillary thyroid carcinoma with diffuse amyloid deposits in the parathyroid and thyroid bed, predominantly within the vasculature. This was confirmed by Congo red staining (Figure 1) with Mayo Clinic sub-typing of AL kappa-type amyloidosis.

Within a month after surgery, she developed worsening lower extremity edema, orthopnea, and paroxysmal nocturnal dyspnea. A repeat echocardiogram showed a decreased ejection fraction of 45-50%, concentric left ventricular hypertrophy, global hypokinesia, and reduced medial and lateral tissue Dopplers, consistent with amyloidosis. The patient was started on diuretics, beta-blockers and ARB, and with modest symptomatic improvement.

The patient was referred to hematology for further workup and management of systemic amyloidosis. Kappa light chains were elevated in serum and urine with a ratio of 18.59:1 in serum. Bone marrow biopsy confirmed the presence of kappa-restricted plasma cells, which comprised 30% of the bone marrow. The biopsy sample was also stained with Congo red and was positive for vascular amyloid deposition. There was no evidence of renal amyloidosis.

Patient was not a candidate for autologous stem cell transplant due to NYHA Class III heart failure. She was enrolled in a phase III trial for a novel first line therapy for amyloidosis, a humanized immunoglobulin G1 monoclonal antibody called NEOD001 that specifically targets misfolded light chain aggregates and amyloid deposits. It works by neutralizing soluble aggregates and clearing insoluble aggregates from target organs. She was also started on cyclophosphamide, bortezomib, and dexamethasone (CyBorD) therapy. She underwent routine free light chain assay follow-up regularly to monitor her response to this therapy. Her latest follow-up visit was at 12-weeks after study enrollment and the patient continued to have downtrending light chains as well as significant symptomatic improvement.

Discussion

Amyloidosis is a systemic disease resulting from plasma cell dyscrasia that leads to deposition of pathologic, insoluble amyloid fibrils within various tissues and organs, altering their function. The clinical manifestation of amyloidosis depends on the type of misfolded protein and its distribution within the body.¹ This disease most commonly affects people in their 50s-70s and has a reported incidence of 8-10 patients per million person-years.^{1,2} Each type of amyloidosis is associated with different comorbidities—more specifically, light chain amyloidosis is often associated with multiple myeloma and

other B-cell malignancies, such as Waldenstrom macroglobulinemia.³

Systemic amyloidosis commonly presents with vague symptoms of fatigue, weight loss, and dyspnea on exertion. Diagnosis thereby requires a high index of suspicion and is usually made by tissue biopsy of the involved organ with confirmation by Congo red staining showing the red-green birefringence under cross polarized light microscopy. The presence of Ig light chains by protein electrophoresis and immunofixation of serum and urine, as well as serum free light chain assay are also part of the work-up. Bone marrow aspiration and biopsy is often used to confirm amyloidosis and exclude other plasma cell or B-cell malignancies.

Cardiac involvement is typically suspected in patients that develop symptomatic heart failure with preserved ejection fraction. However, patients may also present with systolic dysfunction, similar to our patient. Amyloidosis features include concentrically thickened ventricular walls: more specifically, the mean left ventricle wall thickness greater than 12 mm, thickened valves, dilated atria, granular appearing myocardium, and restrictive physiology. Cardiac MRI and PET may also help in diagnosing when histopathology diagnosis is not possible.⁴

Though reports of thyroid amyloid are rare, autopsy-based studies show that 50% of patients with systemic amyloid have amyloid in their thyroid gland.⁵ In the literature, an association between thyroid disease and multiple myeloma has been reported with studies showing that thyroid disease with duration greater than 10 years increasing risk of the development of multiple myeloma (OR, 2.4, 95% CI: 1.35-4.29).⁶

Treatment of systemic amyloidosis varies based on risk stratification. Per Palladini, *et al*⁷ low-risk patients include those younger than 65, less than two organs involved, BNP less than 332, troponin less than 0.035, creatinine clearance above 50%, and systolic blood pressures above 90 mmHg. High-risk patients are those with advanced cardiac amyloid, BNP above 332, troponin above 0.035, and NYHA Class III or IV. Our patient was in the high-risk category due to her elevated BNP, advanced age, and NYHA Class III. Low-risk patients may be considered for autologous stem cell transplant, whereas high-risk patients, like our patient, will need chemotherapy similar to that used in treating multiple myeloma.⁷ Treatment for cardiac amyloidosis is mostly supportive care aimed at symptom reduction. Diuretics may be used, but beta-blockers, ACE inhibitors, and digoxin are generally avoided. Cardiac devices may help symptomatically for end-stage heart failure, but they have not been shown to improve survival.⁸

Our patient was enrolled in a phase 3 randomized, double-blind, placebo-controlled clinical trial, which randomized patients to either receiving a humanized immunoglobulin G1 monoclonal antibody in addition to standard of care CyBORd therapy or CyBORd alone. The G1 monoclonal antibody specifically targets misfolded light chain aggregates and amyloid deposits and improves their clearance. In the phase I/II of this study, 27 patients with AL amyloidosis were treated without significant adverse effects. For those with cardiac amyloid, 50% of the

patients had cardiac response and 50% had disease stabilization, represented by reduction in BNP. For patients with renal impairment, 43% achieved renal response and 57% achieved disease stabilization with reduction in 24-hour urine protein.⁹ The primary outcome of the phase III ongoing study is time to all-cause mortality or cardiac hospitalization. The secondary outcomes are best BNP response, time to cardiac mortality or hospitalization, change in 6-minute walk test, change in cardiomyopathy questionnaire, renal best response, and hepatic best response.⁹ This is the only currently open phase III study in the US to our knowledge for amyloidosis in the front-line setting.

While the current gold standard therapy for treating AL systemic amyloidosis is targeting the plasma cells that overproduce the light chains, it does not directly address the light chain aggregates and deposited amyloid. NEOD001 may change management of plasma cell dyscrasias by directly targeting the amyloid protein, which in turn may improve prognosis for this devastating disease.

Figures

Figure 1. Parathyroid, thyroid bed with amyloid deposits. Congo red stain shown (Figure 1A) and H&E (Figure 1B).

Figure 1A.

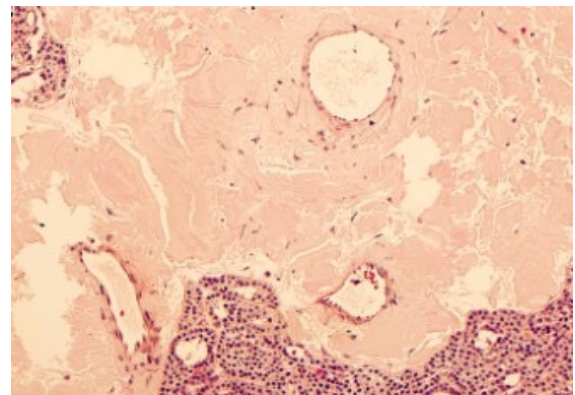
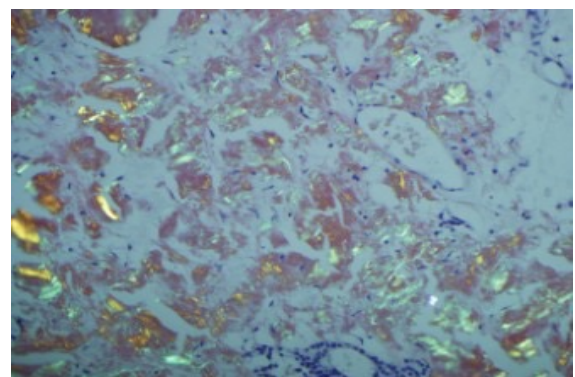


Figure 1B.



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