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A Case of T-Cell Large Granular Lymphocytic Leukemia and Renal Immunoglobulin Heavy Chain Amyloidosis

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Conflict of interest: None declared

Patient: Female, 57

Final Diagnosis: Renal heavy chain amyloidosis

Symptoms: Fatigue • proteinuria

Medication: —

Clinical Procedure: Chemotherapy, consideration of autologous stem cell transplant

Specialty: Hematology

Objective: Rare disease

Background: T-cell large granular lymphocytic leukemia (T-LGL) is a rare hematological malignancy that currently has no standard therapy. Immunoglobulin heavy chain amyloidosis (AH) involving the kidney is a rare condition and the pathology, diagnosis, clinical characteristics, and prognosis are becoming understood. This report is of a rare case of T-LGL associated with renal AH and discusses the approach to management.

Case Report: A 57-year-old woman presented with symptoms of fatigue and she had proteinuria. A diagnosis of T-LGL associated with renal AH was made, which is an association that has not been previously reported in the literature. Given the dysregulation of her immune function due to her underlying T-LGL and her comorbidities, treatment options were limited. She was clinically stable and was initially observed. After one year, her symptoms of fatigue became worse, and her proteinuria increased. Treatment was initiated with the triple drug combination of bortezomib, cyclophosphamide, and dexamethasone (CyBorD) with consideration for future hematopoietic stem cell transplantation (HSCT). Her clinical condition improved, with a reduction in proteinuria.

Conclusions: A rare case of T-LGL and renal AH is presented. Currently, there is no standard therapy for T-LGL and AH amyloidosis, and the approach, in this case, was to manage the patient initially with CyBorD triple chemotherapy.

MeSH Keywords: Amyloid • Antigens, CD98 Heavy Chain • Leukemia, Large Granular Lymphocytic

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Background

In heavy chain amyloidosis (AH), fibrils derived from a truncated immunoglobulin heavy chain deposit in the kidney resulting in proteinuria, and the diagnosis usually requires a renal biopsy [1]. T-cell large granular lymphocytic leukemia (T-LGL) is a rare hematological malignancy that currently has no standard therapy. This report is of a rare case of T-LGL associated with renal AH and discusses the approach to management.

Case Report

In February 2017, a 57-year-old woman presented with symptoms of fatigue, nausea, weight gain, and dyspnea on exertion, and progressive proteinuria. She denied frequent infections, bleeding or bruising. A cardiac workup, including a recent cardiac stress test, was negative. She denied any symptoms of carpal tunnel syndrome but reported vague arthritis pain, both constipation and diarrhea in keeping with irritable bowel syndrome, and occasional episodes of choking. Her family history included a father with a diagnosis of Hodgkin's lymphoma and melanoma and a sister with a history of chronic multiple myeloma. Table 1 is a summary of the patient's laboratory findings at her initial presentation to our clinic in February 2017.

In her past medical history, she had been diagnosed with hypertension for several years. In 2002, she presented with lymphocytosis of 40–50%, which gradually increased to 70%, with mild neutropenia (between 900–1,200/µL), but with normal platelet and hemoglobin levels. A diagnosis of T-cell large granular lymphocytic leukemia (T-LGL) was made, which was never treated. In 2004, she was diagnosed with chronic kidney disease (CKD), which was attributed to chronic hypertension. Between May 2015 and October 2016, her proteinuria increased from 0.5 g/day to 1.5 g/day. A renal biopsy was performed at an external institution in November 2016 that showed glomerulosclerosis and extensive glomerular deposits of eosinophilic material that stained positively with the histochemical stain, Congo red, consistent with a diagnosis of renal amyloid. The renal histology also showed interstitial fibrosis, and moderate arterial and arteriolar sclerosis, consistent with hypertensive nephropathy. A diagnosis of renal amyloidosis was made. Table 2 shows the 24-hour urine protein measurements between 2015 and 2018.

At her initial presentation, a bone marrow aspirate and bone marrow biopsy were both negative for the presence of amyloid. Kappa and lambda free light chains (FLC) were 15.7 mg/L and 27.3mg/L, respectively. Serum immunofixation (SIFE) demonstrated an IgM kappa and free lambda light chains (LCs), and urine immunofixation (UIFE) showed free lambda LCs. The bone marrow biopsy contained two populations of plasma cells, 10–15% IgG lambda, and 5% IgG kappa. Flow cytometry of the bone marrow cells, using immunofluorescence, showed <1% of CD38-positive cells. Approximately 58% of the cell population consisted of neoplastic lymphocytes, which were positive for CD45, CD3, CD8, CD16, and CD57 and expressed alpha-beta T-cell receptor antigens with loss of CD7, CD5, consistent with a diagnosis of bone marrow involvement by T-LGL.

The patient's echocardiogram, electrocardiogram (ECG), endoscopy and barium swallow were normal. Pulmonary function testing to evaluate her dyspnea was normal. In March of 2017, mass spectrometry on renal tissue samples was performed at the Mayo Clinic and confirmed a diagnosis of immunoglobulin heavy chain amyloidosis (AH). The amyloid deposits were mostly restricted to the glomeruli and displayed gamma 1 heavy chain restriction with no other findings of paraprotein disease. Moderate chronic changes of the parenchyma were seen, including glomerulosclerosis.

At her initial evaluation at our clinic, the patient had symptoms of depression, and she commenced treatment with bupropion, which initially improved her symptoms and function. She returned to work, and given that there are no standard treatment guidelines we recommended initial observation. Following initial treatment by observation alone, over a year, her symptoms of fatigue returned with associated proteinuria (Table 2), and treatment was initiated with the triple drug combination of bortezomib, cyclophosphamide, and dexamethasone (CyBorD) with ongoing consideration of future hematopoietic stem cell transplantation (HSCT).

Discussion

Amyloid fibrils consist of monoclonal light chains in AL amyloidosis, and the amyloid fibrils in heavy chain amyloidosis, or AH amyloidosis, are from fragments of immunoglobulin heavy chains. Renal involvement is common in both AL and AH amyloidosis. However, there are no standard treatment options for renal AH amyloidosis. In the literature, there have been two previously published reports of patients with renal AH who had a hematologic response following chemotherapy with combined oral melphalan, bortezomib, and steroids and autologous hematopoietic stem cell transplantation (HSCT), but only one had a renal response [2]. In a series of 16 patients with renal AH and AL amyloidosis [3], the majority of patients received chemotherapy with or without HSCT, while clinical observation alone was also an option. In this cohort, cardiac involvement was less common and bone marrow biopsy was less likely to be positive for AH amyloid than in AL amyloid [3]. The median 24-hour urine protein was 5 gm and patients with renal AH amyloid tended to have a better renal

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Table 1. Laboratory results from February 2017.

Hematology	Value	Normal range
White blood cells	8.5	4.0–11.0 k/uL
Hemoglobulin	13.0	11.0–15.0 g/dL
Platelet	283	150–400 K/uL
Neutrophils (%)	11	
Lymphocytes (%)	69	
Monocytes (%)	16	
Eosinophils (%)	3	
Basophils (%)	1	
Neutrophil (#)	0.9	
Lymphocytes (#)	5.8	
Monocytes (#)	1.4	
Eosinophils (#)	0.2	
Basophils (#)	0.1	
Coagulation		
INR	0.9	0.9–1.3
PTT	28.1	25.7–35.7 sec
Chemistry		
Glucose	107	70–139 mg/dL
BUN	18	6–24 mg/dL
Creatinine	0.84	0.57–1.3 mg/dL
Sodium	138	135–145 mEq/L
Potassium	4.3	3.6–5.1 mEq/L
Chloride	105	98–110 mEq/L
CO2	25	20–30 mEq/L
Anion Gap	8	5–18
AST	25	10–42 IU/L
ALT	28	0–54 IU/L
Alkaline phosphatase	116	40–130 IU/L
Bilirubin (total)	0.40	0.2–1.1 mg/dL
Bilirubin (direct)	0.1	0.0–0.3 mg/dL
Total protein	6.3	6.0–8.3 g/dL
Albumin	3.7	3.4–4.8 g/dL
Calcium	9.6	8.5–10.5 mg/dL
Magnesium	2.1	1.6–2.6 mg/dL
Phosphorus	4.0	2.7–4.5 mg/dL
Uric acid	9.3	2. 6–6.0 mg/dL
Immunology		
Kappa light chain	15.7	3.3–19.4 mg/L
Lambda light chain	27.3	5.7–26.3 mg/L
Kappa/Lambda ratio	0.58	0.26–1.65
Immunoglobulin A	217	70–360 mg/dL
Immunoglobulin G	702	540–1822 mg/dL
Immunoglobulin M	80	22–293 mg/dL
SPEP/SIFE	Trace IgM kappa, additional small lambda light chain without corresponding heavy chain	
Other tests		
B natriuretic peptide	35	0–100 pg/ML
Pro BNP	149	
Troponin I	0.01	0.00–0.03 ng/ML
UPEP/UIFE	Moderate proteinuria, predominantly albumin. Restricted band in the lambda region consistent with monoclonal free light chains.	

BNP – B natriuretic peptide; UPEP – urine protein electrophoresis; UIFE – urine immunofixation; SPEP – serum protein electrophoresis; SIFE – serum immunofixation; INR – international normalized ratio; PTT – partial thromboplastin time; BUN – blood urea nitrogen; AST – aspartate aminotransferase; ALT – alanine aminotransferase.

response and better overall survival when compared with patients with renal AL amyloid (p=0.03) [3].

Currently, treatment for T-cell large granular lymphocytic leukemia (T-LGL) is reserved for patients with symptomatic disease, neutropenia with recurrent infections, symptomatic anemia, thrombocytopenia, or autoimmune conditions. Monoclonal gammopathies can occur in association with T-LGL [4,5], which supports underlying immune dysregulation, which may lead to amyloid deposits in the kidney. There is no

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Table 2. 24-hour urine protein measurements between 2015 and 2018.

Date	24 hour urine protein total
May 2015	500 mg
Oct 2016	1.5 g
Feb 2017	2.5 g (Presented to our clinic)
April 2017	2.0
May 2017	1.3
June 2017	1.5
August 2017	1.6
October 2017	2.6 (Treatment initiated)
July 2018	1.7

standard treatment for symptomatic T-LGL, although immunosuppressive therapy, including methotrexate, cyclophosphamide, and cyclosporine, in combination with prednisone or as single agents, are part of the initial first-line treatment [6,7]. Cyclophosphamide is included in cyclophosphamide, bortezomib, dexamethasone (CyBorD) regimen, which was used in this case to treat both her amyloidosis and T-LGL. Expansion of T-LGL with progressive pancytopenia and repopulation of CD8+, CD57+ T-cells has been described following allogeneic HSCT [8,9], but the current consensus is that HSCT does not have a role in the treatment of T-LGL [6]. There have been several previously published cases of patients with AH with an underlying lymphoplasmacytic lymphoma [3,10,11]. In 2007 Picken et al. [1] commented that AH amyloidosis is almost always associated with some form of plasma cell or B-cell lymphoproliferative process.

In October 2017, the patient's proteinuria increased to >2.5 g/day and she reported symptoms of increased fatigue, dyspnea on exertion, and lower extremity edema. Given her symptoms of irritable bowel syndrome and neuropathic symptoms, she was not an ideal candidate for bortezomib, lenalidomide, or cyclophosphamide due to the side effect profile associated with these agents. Aggressive therapy with HSCT with a CD34-selected autograft focusing on the most primitive progenitor cells might reduce the risk of T-LGL progression.

Daratumumab is a human monoclonal antibody that binds to CD38 and has been reported to result in rapid responses in patients with multiple myeloma and has been reported safe and effective in patients with AL amyloidosis [12–14]. Daratumumab has been shown to be effective in a case of refractory T-cell lymphoma [15], but there is no data on its activity in T-LGL. Although treatment with daratumumab would have been well tolerated and had the potential to treat her T-LGL and heavy chain amyloid, daratumumab therapy was declined by the patient's medical insurer and so she was treated with CyBorD. Currently, the patient is undergoing symptomatic treatment and has improved hematologically with a reduction in 24-hour proteinuria to 1.7 g/day (Table 2).

Conclusions

This report has described a rare case of T-cell large granular lymphocytic leukemia (T-LGL) and immunoglobulin heavy chain amyloidosis (AH) involving the kidney. Currently, there is no standard therapy for T-LGL, and treatment, in this case, was with the triple drug combination of bortezomib, cyclophosphamide, and dexamethasone (CyBorD), with ongoing consideration of future hematopoietic stem cell transplantation (HSCT). Renal AH is an uncommon form of amyloidosis, and as this case demonstrated, mass spectrometry is a helpful proteomic diagnostic method for confirming the diagnosis of renal immunoglobulin heavy chain amyloidosis and in differentiating between AH and AL. This case report has supported previous findings that patients with renal heavy chain amyloidosis typically have no cardiac involvement, less Congo red positivity of the bone marrow, and have improved survival. As novel therapeutic agents become available, it is anticipated that improved treatments for amyloidosis and for T-LGL will improve patient prognosis.

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