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Granulomatous interstitial nephritis secondary to chronic lymphocytic leukemia/small lymphocytic lymphoma☆,☆☆

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ABSTRACT

Granulomatous interstitial nephritis (GIN) is an uncommon pathologic lesion encountered in 0.5% to 5.9% of renal biopsies. Drugs, sarcoidosis, and infections are responsible for most cases of GIN. Malignancy is not an established cause of GIN. Here, we report a series of 5 patients with GIN secondary to chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). Patients were mostly elderly white males with an established history of CLL/SLL who presented with severe renal impairment (median peak serum creatinine, 7.3 mg/dL), leukocyturia, and mild proteinuria. One had nephromegaly. In 2 patients, the development and relapse of renal insufficiency closely paralleled the level of lymphocytosis. Kidney biopsy in all patients showed GIN concomitant with CLL/SLL leukemic interstitial infiltration. Granulomas were nonnecrotizing and epithelioid and were associated with giant cells. One biopsy showed granulomatous arteritis. One patient had a granulomatous reaction in lymph nodes and skin. Steroids with/without CLL/SLL–directed chemotherapy led to partial improvement of kidney function in all patients except 1 who had advanced cortical scarring on biopsy. In conclusion, we report an association between CLL/SLL and GIN. Patients typically present with severe renal failure due to both GIN and leukemic interstitial infiltration, which tends to respond to steroids with/without CLL/SLL–directed chemotherapy. The pathogenesis of GIN in this clinical setting is unknown but may represent a local hypersensitivity reaction to the CLL/SLL tumor cells.

1. Introduction

Granulomatous interstitial nephritis (GIN) is a distinct morphological variant of interstitial nephritis defined histologically by the presence of interstitial inflammation and 1 or more interstitial granulomas [1,2]. Granulomas are composed of activated macrophages, also called "epithelioid cells," with or without giant cells. The renal biopsy incidence of GIN ranges from 0.5% to 5.9% [1-5]. In our experience, GIN accounts for 26% of cases of acute interstitial nephritis [6]. Most cases of GIN in the developed countries are due to drugs or sarcoidosis [1,2], whereas infections, particularly by mycobacteria or fungi, are the most common etiology in the developing countries [4]. Antibiotics and nonsteroidal anti-inflammatory drugs are the most frequent classes of drugs to cause GIN [1,2], although there have been many case reports of GIN linked to other therapeutic agents, including analgesics, diuretics, anticoagulants, and others (reviewed in Javaud et al [2]).

Chronic lymphocytic leukemia (CLL) is the most common leukemia in developed counties and is characterized by progressive accumulation of functionally incompetent B lymphocytes. Chronic lymphocytic leukemia/small lymphocytic lymphoma (SLL) cells have a characteristic immunophenotype, which is a key for diagnosis: they express B-cell–associated antigens CD19, CD20 (weak), and CD23; CD5, a T-cell–associated antigen; and low-intensity surface immunoglobulins (usually immunoglobulin M) with only 1 immunoglobulin light chain (κ or λ). When CLL cells involve lymph nodes without substantial peripheral blood involvement (B-cell count $<5 \times 10^9$/L), the disease is referred to as the "SLL" variant [7]. Most patients with CLL/SLL are asymptomatic at diagnosis, but some present with painless lymph node swelling, weight loss, fevers, night sweats, and/or fatigue. Patients with CLL/SLL have dysfunction of their immune system leading to acquired immunodeficiency and development of autoimmune disorders. Important complications of CLL/SLL include infections, anemia, thrombocytopenia, and increased risk of second cancer.

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Although leukemic infiltration of the kidney is seen on autopsy in most patients with CLL/SLL [8,9], clinical kidney dysfunction is uncommon [10]. Several glomerular lesions pathogenically related to CLL/SLL have been described, including membranoproliferative glomerulonephritis [11-13], minimal change disease [11], immunotactoid glomerulopathy [10,14], cryoglobulinemic glomerulonephritis [13,15], proliferative glomerulonephritis with monoclonal immunoglobulin G deposits [16], membranous glomerulopathy [13,17], and amyloidosis [18]. Expanding the spectrum of renal lesions associated with CLL/SLL, we report the first series of GIN secondary to CLL/SLL. The clinicopathologic features, outcomes, and possible pathogenetic mechanisms of this underrecognized complication of CLL/SLL are discussed.

2. Results

2.1. Clinical histories

2.1.1. Case 1

During a routine follow-up visit in December 2007, a 57-year-old man was noted to have renal insufficiency (Table 1). He had a known history of CLL Rai stage I, ZAP70 and CD38 positive, diagnosed in December 2005, which was followed without treatment. His admission medications were cimetidine, ranitidine, and Tums. He took 2 doses of Aleve 2 days before admission but none prior. On examination, there were nontender 2- to 3-cm nodes along anterior cervical chain, bilateral axillary, and inguinal adenopathy. No organomegaly was identified. Laboratory data showed a hemoglobin level of 15.2 g/dL, white blood cell (WBC) count of 29.0 $\times$ 10^9/L with 90% lymphocytes, platelet count of 149 $\times$ 10^9/L, serum C3 67 and serum C4 23, a total urine protein of 1 g/24 hours, and negative serum and urine protein electrophoresis (Table 1). Urinalysis showed 4 to 10 nondysmorphic red blood cells (RBCs)/high-power field (HPF) without WBCs. A renal biopsy was obtained. Over the next 5 years, patient was treated with multiple courses of chemotherapy, which lead to an improvement in kidney function, but experienced multiple relapses. As shown in Fig. 1, his renal relapses closely paralleled the level of lymphocytosis.

2.1.2. Case 2

A 74-year-old woman had a history of CLL Rai stage 0 diagnosed in 1998. She presented in August 2002 with acute renal failure. Two weeks before admission, she began to experience fatigue, nausea, diarrhea, and vomiting. On admission, she had a hemoglobin level of 9.5 g/dL, WBC count of 100.6 $\times$ 10^9/L with 91% lymphocytes, and platelet count of 203 $\times$ 10^9/L (Table 1). Testing for cytoplasmic anti-neutrophil cytoplasmic antibodies (C-ANCA) and perinuclear anti-neutrophil cytoplasmic antibodies (P-ANCA) was negative. Urinalysis showed less than 1 RBC/HPF, greater than 100 WBCs/HPF, and occasional hyaline casts. Her admission medications were nitrofurantoin (intermittently for 2 years), spironolactone/hydrochlorothiazide (for many years), and alendronate sodium (for 2 weeks). A renal biopsy was obtained.

She was treated with levofloxacin until urine culture was confirmed to be negative. She was also initially treated with high-dose corticosteroid. Despite this, her renal failure progressed, and dialysis was initiated. One dose of intravenous cyclophosphamide was administered, and the WBC count dropped to 26.7 $\times$ 10^9/L. Patient became dialysis independent after 2 months. Her CLL/SLL remained stable, but she was diagnosed with breast cancer in 2005 and elected not to undergo any treatment. Patient died in March 2005 of complications of breast cancer.

2.1.3. Case 3

A 78-year-old man was admitted for acute on chronic renal failure and severe pruritus in September 2002. He was diagnosed with CLL Rai stage III in 1994 and received intravenous immunoglobulin to treat hypogammaglobulinemia. In May 2002, he was noted to have a serum creatinine of 2.4 mg/dL and a 24-hour urine protein of 242 mg. Afterward, the patient became fatigued and developed rash and severe

Table 1
Clinical data

Case no.	Age/sex/race	CLL/SLL Rai stage at GIN diagnosis	Time from diagnosis of CLL/SLL to GIN in yrs	Baseline SCr (mg/dL)	Peak SCr	SCr at Bx (mg/dL)	Proteinuria (g/day)	Hematuria	Leukocyturia	Other medical conditions	Treatment	Renal outcome	Patient outcome
1	57/M/W	I	2	1.3 (9 mo prior)	6.7	5.9	1	Yes	No	GERD	Steroids, rituximab, cyclophosphamide	Partial recovery (S. Cr 2.3)	Alive (81 mo post-Bx)
2	74/F/W	0	4	NA	18	14.9	0.9	No	Yes	Hypertension, chronic urinary tract infection	Steroids, cyclophosphamide, HD	Partial recovery (S. Cr 2.1)	Died of breast CA (31 mo post-Bx)
3	78/M/W	III	8	2.4 (4 mo prior)	7.3	6.9	0.2	No	Yes	Hypertension, atrial fibrillation	Steroids	Partial recovery (S. Cr 3.2)	Died of cellulitis (2 mo post-Bx)
4	79/M/W	I	18	2.4 (2 mo prior)	6.1	5.7	2.2	Yes (Foley catheter)	NA	BPH	Steroids, rituximab, HD	Partial recovery (S. Cr 2.1)	Died (49 mo post-Bx)
5	63/M/W	IV	4	2 (4 mo prior)	10.2	7	2	No	Yes	Hypertension, diabetes, BPH	Rituximab, HD	ESRD (never recovered)	Alive (43 mo post-Bx)

Abbreviations: *BPH*, benign prostatic hyperplasia; *Bx*, renal biopsy; *CA*, carcinoma; *ESRD*, end-stage kidney disease; *F*, female; *GERD*, gastrointestinal reflux disease; *HD*, hemodialysis; *M*, male; *NA*, not available; *SCr*, serum creatinine; *W*, white.