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Progressive Renal Failure Due to Recurrent Attacks of Polyclonal Light-Chain Cast Nephropathy Induced by Recurrent Chest Infections Ablated by Rituximab

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Abstract

Background: Cast nephropathy is reported only with monoclonal light-chain gammopathy. **The case:** A 38-year-old white male was referred for management of progressive renal failure (serum creatinine at 294 μmol/L). He had cigarette-induced bronchiectasis and 2 attacks of partially resolving acute renal injury associated with chest bacterial infections 2 years and 1 month ago. Ultrasonography revealed 9 cm kidneys with thin and echogenic cortex. Autoimmune diseases and lymphoproliferative disorders/myeloma were excluded by laboratory and radiological tests as well as bone marrow biopsy. Kidney biopsy showed focal segmental glomerulosclerosis with distal tubules studied with PAS-ive casts surrounded by inflammatory cells, and moderate interstitial fibrosis. Immunohistochemical studies did not show glomerular immune deposits, yet antibody to both light chain Kappa and Lambda were detected in those casts and the intratubular epithelial droplets. Hence, after control of his infections and cigarette cessation, he was treated with yearly Rituximab infusions. Despite having 2 subsequent attacks of chest infections, over 2 years of follow-up, he did not experience new renal injury or deterioration. **Conclusion**: In predisposed individuals, recurrent infection can induce polyclonal light-chain cast nephropathy which is amenable to Rituximab.

Keywords

Cast Nephropathy, Multiple Myeloma, Renal Injury, Renal Failure, Melphalan, Kidney Biopsy, Light Chains, Rituximab

1. Introduction

Cast nephropathy (CN) is an acute renal injury due to the precipitation of excessive and pathogenic monoclonal light chains (LC), either Kappa or Lambda, in distal nephrons [1]. Histologically, they form large, angulated, and fractured tubular casts that are associated with 1) acute renal disease due to tubular obstruction and direct toxicity, manifested by vacuolization and peritubular inflammation with syncytial giant cell reaction, as well as 2) chronic interstitial nephritis. Three factors are essential for the development of tubular toxicity associated with CN: 1) heavy load of monoclonal LC that overwhelms its catabolism in proximal tubules, 2) pathogenic casts since some LC are not (viz. monoclonal gammopathy of undetermined significance), and 3) precipitating events (viz. dehydration, infection, hypercalcemia, and use of nephrotoxic agents such as non-steroidal anti-inflammatory drugs and contrast media) [2]. Monoclonal LCs are associated with plasma cell dyscrasias, such as monoclonal gammopathy of undetermined significance, multiple myeloma, lymphoplasmacytic lymphoma/Waldenstrom's macroglobulinemia, or primary amyloidosis. Nearly 90% of patients with monoclonal LCs have overt myeloma, and it is seen in half of myeloma patients with renal disease [2]. Reduction of serum LCs is associated with 50% renal improvement, and failure results in end-stage kidney disease within 8 months [3]. On the other hand, CN due to hypergammaglobulinemia (polyclonal gammopathy) is rare [4]. Normally, 500 mg of polyclonal LCs are produced by the normal lymphoid system and catabolized by proximal tubules. However, hypergammaglobulinemia is due to overproduction of more than one class of immunoglobulins by plasma cells. It is most commonly associated with liver disease, acute or chronic inflammation, autoimmune disorders, and some malignancies [5]. In this case report, we present a patient with recurrent attacks of acute kidney injury that is associated with polyclonal LC gammopathy induced by chest infections yet without multiple myeloma or lymphoproliferative disorder.

2. The Case

A 38-year-old man was referred for evaluation of progressive renal disease in the past 2 years. Except for cigarette-induced bronchiectasis, he did not have a past history of chronic diseases, autoimmune disorders, or long-term drug use. However, he had 2 attacks of partially resolving acute injury associated with chest bacterial infections 2 years and 1 month ago. Both were associated with loin pain, proteinuria, hematuria, and high procalcitonin levels at 6 and 7 ug/ml, respectively (normal < 0.5). Both attacks were treated with intravenous Ceftriaxone 1 g/day for 7 days. During the first attack, his initial serum creatinine was 370 umol/L, which decreased to 180 three months later. Unfortunately, he did not have subsequent work up or follow up since then. In the second attack, his initial serum creatinine was 450 umol/L. He had hypertension (160/110 mm Hg) without lymphadenopathy and edema. Laboratory abnormalities were hemoglobin at 126

g/L, serum creatinine at 294 umol/L with normal serum albumin, globulins, calcium, and creatinine phosphokinase. Serum complements (C3 & C4), IgA, IgG4, and protein electrophoresis were normal. ANA, anti-ds DNA, ANCA, anti-GBM antibodies, RA, hepatitis B surface antigen, and anti-HCV antibodies were negative. Twenty-four-hour urine showed creatinine clearance at 0.6 ml/seconds and protein excretion at 1.4 g/day. Chest x-ray and ECG were normal. Abdominal and pelvic ultrasound was normal except for 9 cm kidneys with an increase in kidney cortical echogenicity. After control of hypertension with daily losartan 50 mg and amlodipine 5 mg as well as exclusion of infection, kidney biopsy was done. It showed 13 glomeruli, 10 of which had global sclerosis and 2 showing segmental sclerosis. Proximal tubules had cytoplasmic vacuolation, hyaline inclusions, and scattered PAS-ive casts surrounded by inflammatory cells (Figure 1). Immunoperoxidase stains did not show immune deposits in glomeruli, yet antibody to light chain Kappa was detected in casts and intratubular epithelial droplets (3+) and that to Lambda (2+) (Figure 2). There were no crystals in the casts and Congo red stain was negative in casts and glomeruli. Moreover, CD138 as well as EMA and Congo red stains were negative. The interstitium showed moderate lymphocytic infiltrate and fibrosis at 30%. The vasculature was unremarkable. Serum protein electrophoresis and urine immunoelectrophoresis did not show monoclonal

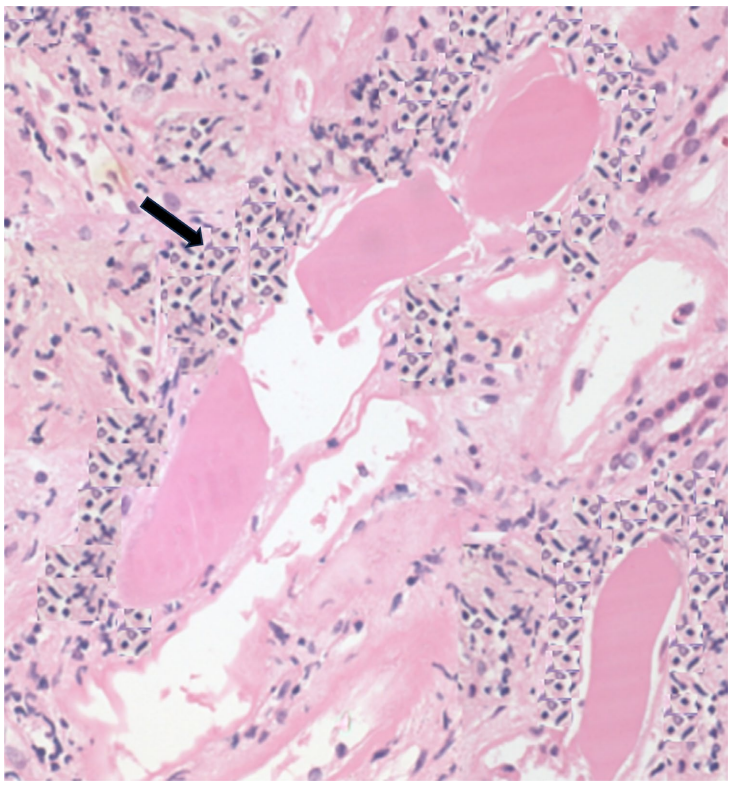


Figure 1. Photomicrograph of a kidney biopsy showing large, angulated, and fractured eosinophilic tubular casts surrounded by mononuclear and plasma cells, eosinophils (Arrow) associated with acute tubular injury with vacuolization of the cytoplasm, flattening of the epithelium, and loss of brush borders (H&E ×400).

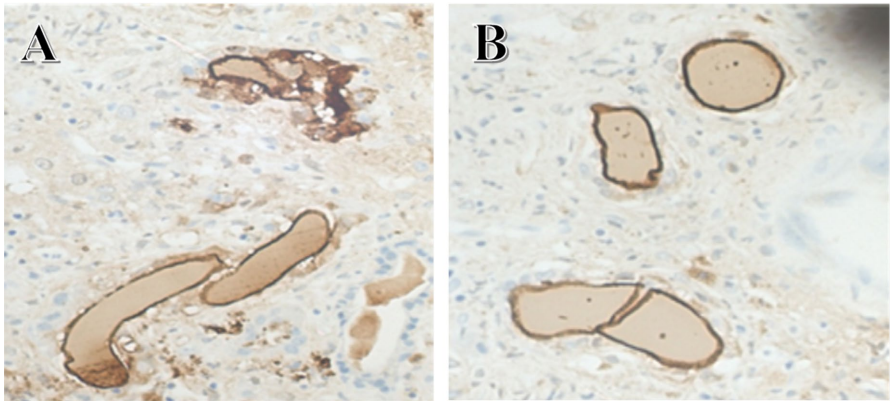


Figure 2. Photomicrograph of a kidney biopsy showing monoclonal staining of the casts for both Kappa (A) and Lambda (B) in the large tubular casts (H&E ×400).

spikes. Kappa free light chain level was 5× upper limit of normal while that of Lambda was 3×, yet their ratio was normal. Whole body computerized tomography did not show any lytic lesions. Bone marrow aspirate and trephine biopsy failed to show an increase in plasma cells in bone marrow or lymphoproliferative disorders. Based on the above data, the patient was diagnosed as having recurrent infection-induced cast nephropathy. Hence, he was treated with yearly Rituximab infusions (R) at a dose of 1 g followed by 1 g 2 weeks later. Moreover, he was instructed to adhere to a low sodium, potassium, and protein diet. Up to 2 years of follow up, he did not experience disease recurrence, medication side effects, or renal deterioration (**Table 1**).

3. Discussion

Historically, polyclonal LCs were not associated with renal disease except for rare cases of immune complex-induced membranoproliferative glomerulopathy [6]. In chronic antigenic stimulation, interleukin 6 activates naïve $CD4^+$ T cells to become helper cells, which leads to B cell proliferation and subsequent immunoglobulin secretion [7]. Previous studies have suggested that genetic predisposition plays a vital role in the extent of immune response in various populations [8]. Moreover, polyclonal serum free light chain elevation is associated with increased risk of monoclonal gammopathies and chronic antigenic stimulation in predisposed individuals [9]. Our patient presented with a rare event of CN due to polyclonal LC hypergammaglobulinemia secondary to recurrent chest infections. Despite amelioration of his renal disease with antibiotic therapy, it was progressive with subsequent attacks following chest infections. The disease was confirmed by 1) laboratory testing that lacked monoclonal bands, high kappa and lambda LCs with normal ratio, and 2) kidney biopsy that showed pathological lesions of CN associated with both LCs without amyloidosis and crystal formation [10]. The initial management of hypergammaglobulinemia (polyclonal gammopathy) indicates eradication of its underlying culprit. However, in predisposed patients for polyclonal LC disease viz. autoimmune disorders, chronic liver disease, and

Table 1. Flow chart of demographical data and biochemical changes of a patient with polyclonal cast nephropathy before and after Rituximab therapy.

	Time (months)					
	-24	-21	0	1	12	24
Age, gender & race: 38 years, male, White						
Clinical data:						
Main complaint:	Chest infection	Follow up	Chest infection	Follow up	2 chest infections	
Blood pressure: (120-80 mm Hg)	150/100	140/90	150/100	160/110	120/80	120/80
Body weight: (Kg)	58	58	60	62	63	62
Laboratory tests:						
Hemoglobin:						
(130-160 g/L)	110	110	126	95	115 g/L	110 g/L
Serum:						
Creatinine: (60-120 umol/L)	370	180	616	294	302	284
Albumin: (35-50 g/L)	34	35	29	31	37	39
Free light chain Kappa: (3-19 mg/L)	ND	ND	71	52	18	4
Free light chain Lambda: (6-26 mg/L)	ND	ND	54	37	12	6
Kappa/Lambda ratio: (0.3-1.6)	ND	ND	1.3	1.4	1.5	0.6
Procalcitonin (< 0.5 ng/ml)	6	0.3	8	0.2	0.1	0.2
24-hour urinary protein:						
(< 150 mg)	1.6 g	1.2 g	1.8 g	1.4 g	1 g	0.6 g

Ancillary tests: negative for (a) hypercalcemia, (b) autoimmune markers, (C) lytic lesions by CT, (b) SPEF and urine IE for for monoclonal spikes, and (c) increase plasma cells by bone marrow biopsy

Abreviations:

ND: not done, CT: computerized tomography, SPEP: serum protein electrophoresis, IE: immunoelectrophoresis

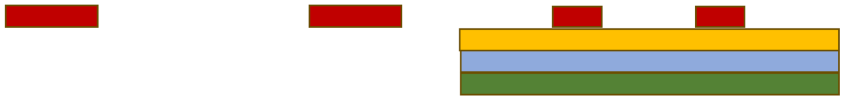
Management:

Ceftriaxone 1 g every 12 hours for 1 week

Losartan 50 mg

Amlodopine 5 mg

Rituximab



Abreviations:

ND: not done, CT: computerized tomography, SPEP: serum protein electrophoresis, IE: immunoelectrophoresis, BM Bx: bone marrow biopsy

recurrent infections, as in our patient, a safe and effective immune-modulating drug is essential to prevent progressive renal disease. Hence, we elected to use R. The drug is a chimeric monoclonal antibody targeted against CD20, a surface antigen present on B cells, thus depleting precursor B cells (new B cells) and memory B cells while sparing plasma cells and hematopoietic stem cells [11]. Its efficacy in autoimmune disease is thought to be due to the decrease in the rate of new plasma cell synthesis (as $CD20^+$ B cells are a required intermediary) or to the disruption of another role of B cells in the immune system, such as their role as antigen-presenting cells to T cells [12]. Hence, it is effective as a maintenance therapy in renal autoimmune disease [13]. In our patient, R was effective in preventing further kidney deterioration and was safe (without exacerbating the patient's recurrent chest infections).

4. Conclusion

Our patient confirms such an association with typical attacks of CN following infections that resulted in progressive renal disease. Moreover, we provided a safe and effective measure, in the form of R, to prevent future ESRD.

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Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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