Severe Acute Interstitial Nephritis: Response to Therapy With Antithymocyte Globulin

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INTRODUCTION

Acute interstitial nephritis (AIN) is an important and common cause of acute kidney injury. The established causes of AIN include drugs, infections, and autoimmune diseases. In a small number of cases, no obvious cause can be identified. The classical presentation of AIN with hypersensitivity symptoms such as skin rash, eosinophilia, and fever, largely induced by antibiotics, has been replaced mainly by less classical manifestations in elderly patients with nonsteroidal antiinflammatory agents and proton pump inhibitors as the offending agents. Drug-induced AIN remains the most common etiology of AIN; however, it is important to include other entities such as tubulointerstitial nephritis with uveitis syndrome, IgG4-related disease, systemic lupus erythematosus, sarcoidosis, and other systemic diseases in the differential diagnosis. AIN is characterized histologically by heavy interstitial infiltrate of inflammatory cells mainly T-lymphocytes and macrophages, with variable numbers of plasma cells, eosinophils, neutrophils, and noncaseating granulomas. The infiltrates can be patchy or diffuse and are concentrated in the deep cortex and the outer medulla. In addition to infiltrative lesions and interstitial edema, tubular lesions range from mild cellular changes to widespread epithelial cell necrosis. Traditionally, the treatment consists of the removal of the offending drugs, if known, along with steroid therapy. Steroids are administered as high doses and followed by a rapid taper. Corticosteroid-dependent, relapsing AIN continues to be an important therapeutic challenge in the treatment of AIN. The present report indicates that therapy specifically targeted at the T cells using antithymocyte globulin (ATG) can dramatically alter the course of the disease, in some cases.

CASE PRESENTATION

The patient is a 43-year-old woman with a medical history of bipolar disorder, untreated hepatitis C, substance abuse, and psoriasis, who presented in July 2014 with a 4-day history of nausea, vomiting, diarrhea, and acute kidney injury with a serum creatinine of 1170 μmol/l. Renal ultrasound demonstrated normal-sized kidneys without hydronephrosis. Both infectious and malignancy workup were negative, and there were no offending drugs identified in the history or toxicology screen. Her serology revealed low C3 of 0.63 (reference 0.79–1.52), normal C4, and a positive cytoplasmic antineutrophil cytoplasmic antibody with anti-PR3 of 10.8 (reference < 3.5). Antinuclear antibody was 1.1 (reference #1.0) and anti-DNA antibody was normal. Furthermore, the patient did not fulfill the clinical criteria for systemic lupus erythematosus.

She was admitted with a diagnosis of acute kidney injury. Her renal biopsy showed AIN with a predominantly lymphocytic infiltrate (Figure 1a and c). The immunofluorescence microscopy showed 12 glomeruli with mesangial staining for IgA (1+), IgM (trace), C3 (1+), kappa (trace) and lambda (trace to 1+), and no staining for IgG. Electron microscopy showed a heterogeneous cellular infiltrate in the interstitium composed of activated lymphocytes and occasional plasma cells. It was accompanied by acute degenerative changes in the tubular cells, including marked alterations of the brush border. Occasional electron-dense deposits were found with a coarse granular structure, not typical of immune deposits. Overall, the
electron microscopy showed features consistent with a diagnosis of interstitial nephritis and no evidence of glomerular changes associated with ANCA vasculitis or systemic lupus erythematosus. The etiology of the AIN remained unclear, and hemodialysis and pulse steroid therapy (500 mg IV for 3 days, followed by 65 mg PO daily) were instituted. There was no evidence of uveitis. As there was no improvement, mycophenolate 500 mg 3 times daily was added. She remained hemodialysis dependent and was otherwise well. As there was no etiological basis identified, and as she tolerated the therapy well, treatment was continued longer than usual. A renal ultrasound was obtained to establish whether chronic changes had occurred, and as the renal size was unchanged and as there was no increased echogenicity, a repeat renal biopsy was carried out 4 months after the initial presentation. The second biopsy appeared very similar to the first, with a prominent cellular infiltrate and little scarring (the P value for the number of T-lymphocytes between biopsy 1 and 2 was 0.125). The levels of the third and fourth components of complement had normalized, the ANCA assay was negative on 2 occasions, the extractable nuclear antigen antibodies screen was negative, the anti-DNA AB was normal, and serum IgG was within the normal range. As T cells remained the predominant cells in the infiltrate, she was admitted for specific anti-T-cell therapy. She received a total of 600 mg (10 mg/kg) of rabbit ATG (Thymoglobulin, Sanofi-Aventis, Laval, PQ, Canada) in 8 infusions from 29 November to 9 December 2014. Hemodialysis was no longer necessary 2 months after the initiation of ATG therapy, and her serum creatinine continued to fall (from the 400 range, while on chronic hemodialysis) and reached its nadir 10 months after the final antithymocyte globulin infusion. The serum creatinine remained stable in the 140 μmol/l range. At this time she was receiving 15 mg of prednisone daily and 720 mg of mycophenolate twice daily. To establish

Figure 1. (a) Renal biopsy before treatment on 18 July 2014 (hematoxylin and eosin stain). (b) Renal biopsy after treatment on 18 April 2016 (hematoxylin and eosin stain). (c) T-lymphocyte interstitial infiltrate before treatment. The mean number of T cells per mm² is 3835 ± 436 (CD3 immunohistochemical marker). (d) T-lymphocyte infiltrate after treatment (CD3 immunohistochemical marker). The mean number of T cells per mm² is 663 ± 184 (P < 0.0005) (CD3 immunohistochemical marker).
whether there was continued diffuse ongoing inflammation accounting for the remaining renal function impairment (requiring additional therapeutic intervention), a third biopsy was carried out 16 months after completion of the ATG infusions. This indicated a patchy infiltrate of lymphocytes in the interstitium, with a marked decrease in the density of T-lymphocytes that were evaluated by quantitative immunohistochemistry (Figure 1b and d) (Table 1). Additional immunohistochemical characterization (not illustrated) of the cell populations in the inflammatory cell infiltrate in the pretreatment biopsy showed that the large majority of the T cells were T helper cells, whereas T suppressor cells were present in a smaller proportion, with an approximate ratio of 9 to 1, respectively. Plasma cells, identified with the CD138 marker, were rare. In addition, cells of the monocytes/macrophages lineage, identified with the CD163 marker, were present at high frequency in the interstitial infiltrate. There was no significant number of natural killer cells. After the ATG treatment, there was a marked and parallel decrease in T helper cells, T suppressor cells, and monocytes/macrophages.

### DISCUSSION

The main aim in the treatment of AIN is to arrest the inflammatory reaction, by removing the inciting agent, and depleting the inflammatory cells from the renal parenchyma. In this respect, corticosteroids are frequently used, but the effectiveness of their role remains controversial.\(^7\)\(^,\)\(^9\)\(^,\)\(^10\) AIN is postulated to be an immune-mediated disorder driven by T cells primarily. Therefore, an immunosuppressive regimen using corticosteroids is the commonly used treatment for AIN. Corticosteroids exert their antiinflammatory effects by interrupting multiple steps in signal transduction pathways given the ubiquitous expression of glucocorticoid receptors. Corticosteroids function by activating glucocorticoid receptors to directly or indirectly regulate the transcription of target genes to inhibit antigen presentation, cytokine production, and proliferation of lymphocytes.\(^11\) In this case, after a period of lack of response to steroids, mycophenolate was added to her therapy. Mycophenolate exerts its immunosuppressive effects through the inhibition of the rate-limiting enzyme in the de novo pathway of purine synthesis and in turn decreases T- and B-lymphocyte proliferation and reduces antibody production.\(^12\) ATG is a purified polyclonal Ig, directed against human thymocytes. The mechanism of action on the immune response is not fully understood; however, its primary mechanism is through T-cell depletion by inducing lymphocyte depletion in the peripheral blood by complement-dependent cell lysis.\(^13\)

In the present case, there was little impact of therapy with steroids and mycophenolate. However, we observed an 80% decrease in the density of T-lymphocytes in the interstitium after ATG therapy coupled with a dramatic and sustained improvement in the renal function, allowing cessation of hemodialysis.

No clinically significant side effects of the ATG therapy were observed during the treatment of the patient. Hematological studies showed however that there was a 56% decrease (1.221–0.54 × 10^9/L) in the number of circulating lymphocytes, as might be expected from the cellular target of the drug.

To conclude, the present report is the first to show a dramatic response to ATG therapy in a patient with acute interstitial nephritis who was previously steroid resistant and hemodialysis dependent. The most recent serum creatinine (4 August 2016) was 125 µmol/l. This case raises the concern that perhaps patients with potentially reversible disease remain on hemodialysis, due to failure to respond to initial conventional therapy. Such patients, if an ultrasound suggests the absence of chronic changes, should undergo a repeat renal biopsy to identify the possible target for more specific therapy.

### DISCLOSURE

All the authors declared no competing interests.

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