The Critical Role of Therapeutic Plasma Exchange in the Treatment of MPO-ANCA Associated Crescentic IgA Nephropathy

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Crescentic IgA nephropathy (IgAN) with the positivity for antineutrophilic cytoplasmic antibody (ANCA) is a novel and uncommon entity. The optimal management of this condition is not well-defined. We report a 49-years-old woman with complaints of skin rash and swelling of lower limbs. She had hematuria, proteinuria and, progressive renal impairment with positive myeloperoxidase (MPO)-ANCA test. A renal biopsy revealed MPO-ANCA-associated crescentic IgAN. Induction therapy was intravenous methylprednisolone, cyclophosphamide and, therapeutic plasma exchange (TPE). An unexpected disease flare-up was observed during induction immunosuppressive therapy which regressed after long-term TPE. The patient experienced a full renal recovery after treatment with long-term TPE, cyclophosphamide, and corticosteroids.

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Case Report

INTRODUCTION

Crescentic IgA nephropathy (IgAN) with the positivity of antineutrophilic cytoplasmic antibody (ANCA) is a novel and uncommon condition with no well-defined management. [1, 2] Glucocorticoids and cyclophosphamide have shown benefits. [3, 4, 5] However, the effectiveness of therapeutic plasma exchange (TPE) has not been evaluated in the aggressive form of the disease. Here we describe a patient with ANCA-associated crescentic IgAN whose kidney function deteriorated under induction therapy of Glucocorticoid plus Intravenous Cyclophosphamid*e* which emphasizes the therapeutic role of *TPE.*

CASE REPORT

A 49-year-old woman complained of fatigue, rash and, swelling of lower limbs for two weeks. Physical examination revealed maculopapular rash on both extremities and pretibial edema. Laboratory results were as follows: leukocyte, 5900 /mm3; hemoglobin, 7.6 g/dL; serum creatinine, 4.3 mg/dL; urea, 92 mg/dL; albumin, 3.1 g/dL; C-reactive protein, 43 mg/L (normal range, 0.00 to 5.00); urine microscopy: 83 erythrocytes, 9 leukocytes per high-power field; proteinuria, 2.1 g/d. The results of serum antinuclear antibody, anti-glomerular basement membrane antibody, complement and, immunoglobulin levels were normal. ANCA test was 26.4 U/ml for myeloperoxidase (MPO)-ANCA (normal ranges, < 5 U/mL). She was treated with methylprednisolone 1 g daily for three days. Then she received oral methylprednisolone 64 mg once daily. A kidney biopsy was performed. Pathology reported crescentic IgAN (Figure 1, Table 1). Anti MPO antibody and pathology were compatible with the diagnosis of MPO-ANCA-associated crescentic IgAN. She received 750 mg of intravenous

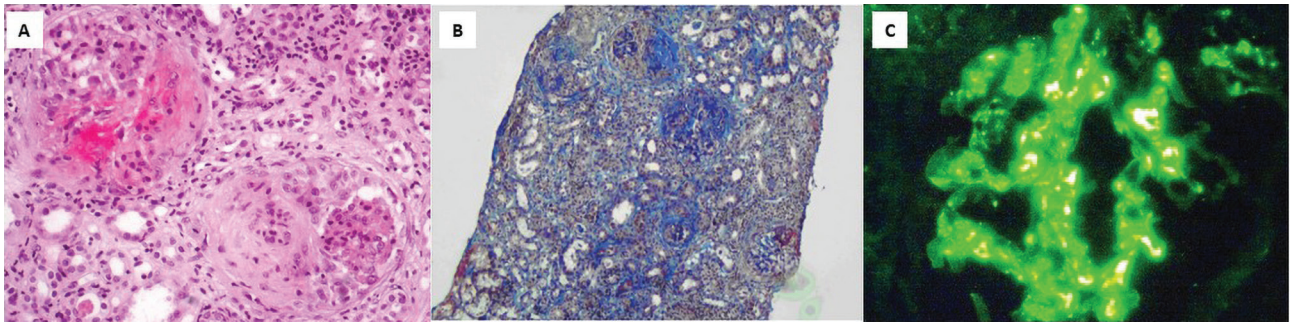

Figure 1. Pathology reported crescentic IgAN.

Table 1. Histopathological findings of the patient based on Oxford classification

Mesangial hypercellularity: M1
Glomeruli showing segmental sclerosis: S0
Endocapillary hypercellularity: E1
Cellular/fibrocellular crescents: 25/32
Tubular atrophy/interstitial fibrosis: T0
Arteriosclerosis: None

cyclophosphamide). Due to the worsening of kidney function, hemodialysis was started. TPE was initiated with fresh frozen plasma every other day. After five TPE sessions, the patient's rash completely resolved, MPO-ANCA level returned to normal, and creatinine regressed to 2.3 mg/dL. One week after completion of the induction immunosuppressive therapy, maculopapular rash reappeared on her lower legs with a progressive increase of serum creatinine. We decided to continue TPE to 10 sessions. Subsequently, her serum creatinine fell to 2.1 mg/dL and, the rash disappeared. After taking the second 750 mg dose of cyclophosphamide, the patient was discharged at week 9 with methylprednisolone 64 mg/d tapered over six months to a maintenance dose of 4 mg/d. The maintenance therapy was started with Azathioprine 50 mg/d and methylprednisolone after the third dose of cyclophosphamide, and continued at week 72. On the latest follow-up at month 30, her serum creatinine, albumin, and urinary protein levels were 1.15 mg/dL, 4.3 g/dL, and 100 mg/d, respectively (Figure 2).

DISCUSSION

Our knowledge regarding the management of ANCA-associated crescentic IgAN is limited. Haas *et al*. described improvement in three patients with ANCA-positive crescentic IgAN treated with cyclophosphamide and corticosteroids, however,

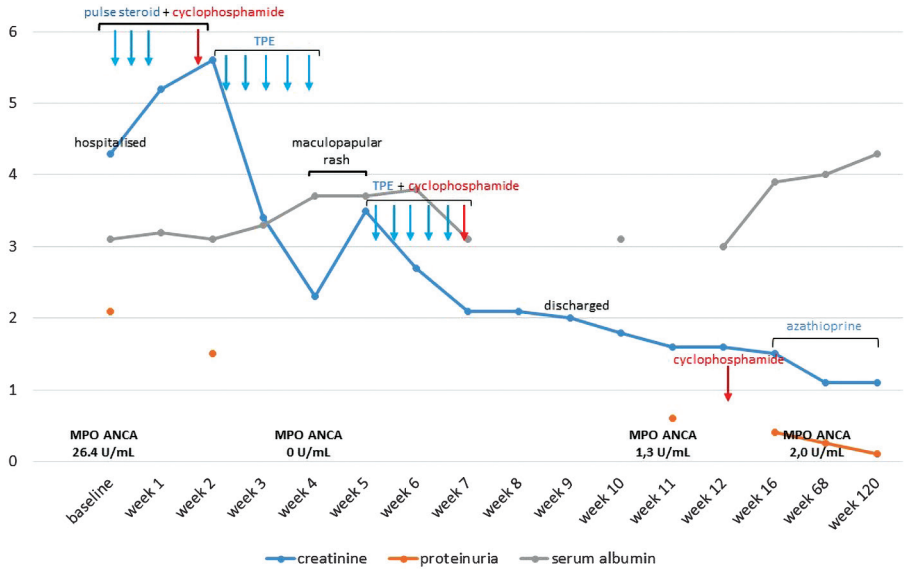

Figure 2. The serum creatinine, albumin, and urinary protein levels were 1.15 mg/dL, 4.3 g/dL, and 100 mg/d, on the latest follow-up.

another two patients required dialysis under therapy.[3] Bantis *et al.* described eight patients with ANCA-associated crescentic IgAN treated with cyclophosphamide and corticosteroids, who experienced an improvement in kidney function.[1] Although, others have observed unsatisfactory responses to treatment.[2,4,6] In one study, Yang *et al.* proposed an initially good response to immunosuppressive therapy among ANCA-positive IgAN patients, however, 40% of them developed end-stage renal disease eventually. [5]

The majority of ANCA-positive IgAN patients, who firstly responded to therapy developed moderate to advanced stages of chronic kidney disease.[1-5, 7, 8]

Plasma exchange may be a potential therapeutic option to achieve complete recovery same as this case. In addition to the immunosuppression, our patient received five sessions of TPE for severe renal impairment. The patient's disease was unexpectedly exacerbated under immunosuppressive therapy with a negative MPO-ANCA test and regressed rapidly after prolonged TPE. A circulating autoantibody other than MPO-ANCA was recently mentioned in ANCA-associated vasculitis. This antibody may have existed in our patient and might have been removed only by prolonged TPE.[9]

The second explanation may be the disease progression by MPO-ANCA titers below the detection limit of current enzyme immunoassay tests. [10, 11] We believe that long-term TPE prevents irreversible kidney injury possibly by removing all circulating antibodies like MPO-ANCA.

The aggressive immunosuppression provided our patient with complete recovery. Only four patients with ANCA-positive crescentic IgAN have been reported to receive TPE in addition to cyclophosphamide and corticosteroids and, three of them remained free from dialysis. [12] Our case is the first report of a patient who suffered from ANCA-positive crescentic IgAN and achieved complete renal recovery after prolonged TPE and immunosuppression.

We can consider TPE as a part of immunosuppressive therapy in patients with ANCA-positive crescentic IgAN, especially in severe cases requiring dialysis at presentation.

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