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'Pauci-immune' Rapidly Progressive Glomerulonephritis Associated with Systemic Vasculitis

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'Pauci-immune' glomerulonephritis has been recognized as an important cause of rapidly progressive glomerulonephritis. The paucity of immune deposits can be separated from the other two major immunohistologic variants of crescentic glomerulonephritis, ie, antiglomerular basement membrane (GBM) antibody-mediated and immune complex-mediated glomerulonephritis.
Here we describe the case of a 42-year-old woman with pauci-immune' glomerulonephritis and vasculitis pressenting as rapidly progressive renal failure with characteristic pathologic and immunohistologic findings. And in this case, despite oliguria and rapid deterioration of renal function, the renal function recovered partially and continued to be stabilized with a favorable response to hemodialysis and combined system immunosuppressive therapy.

Key Words: *Systemic vasculitis, rapidly progressive glomerulonephritis*

INTRODUCTION

Rapidly progressive glomerulonephritis (RPGN) is a relatively rare syndrome, consisting of rapid deterioration in renal function and extensive crescent formation surrounding the majority of glomeruli (Morrin, 1978: Atkins, 1988).

Many types of glomerulonephritis can exhibit crescent formation and occasionally renal failure (Atkins, 1988). Some patients improve after treatment with immunosuppressive drugs, but the response is variable. This is to be expected since rapidly progressive glomerulonephritis is not produced by a single disease. In some cases glomerular injury is caused by autoantibodies to the glomerular basement membrane, however it can be associated with systemic vasculitis or other systemic diseases (Hind, 1983; Serra, 1984; Swerlick, 1989). The kidneys are often involved in systemic vasculitis (Serra, 1984) and the outcome of oliguric renal vasculitis may be fatal (Tuma, 1976).

We describe our experience in managing an acute oliguric crescentic glomerulonephritis. The renal function was improved after hemodialysis and combined prednisolone-cyclophosphamide therapy.

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CASE REPORT

A 42-year-old woman was admitted to our hospital because of fever, chill, and arthralgia. She had been well until about 3 months earlier, when there was the onset of fever, chill, and cough. A physician made a diagnosis of URI and advised analgesics, but without improvement. 3 days before admission she experienced aggravated fever, chill, arthralgia, and papular rashes on the lower legs, and she was admitted to our hospital.

The temperature was 38.3°C, the pulse 86, and the respiration 20. The blood pressure was 130/80 mmHg.

On examination the patient was alert but acutely ill and puffy. Fresh vesicles and crusts were present over the lips. She showed erythematous rashes on both cheeks and multiple purpuric maculae, petechial lesions on the lower legs and forearms (Fig. 1). No lymphadenopathy was seen. The heart and chest were normal. The abdomen was normal; the liver and spleen were not felt. No effusion or limitation of joint motion was found. The neurologic examination was negative.

The urine was yellow, had a specific gravity of 1.025,

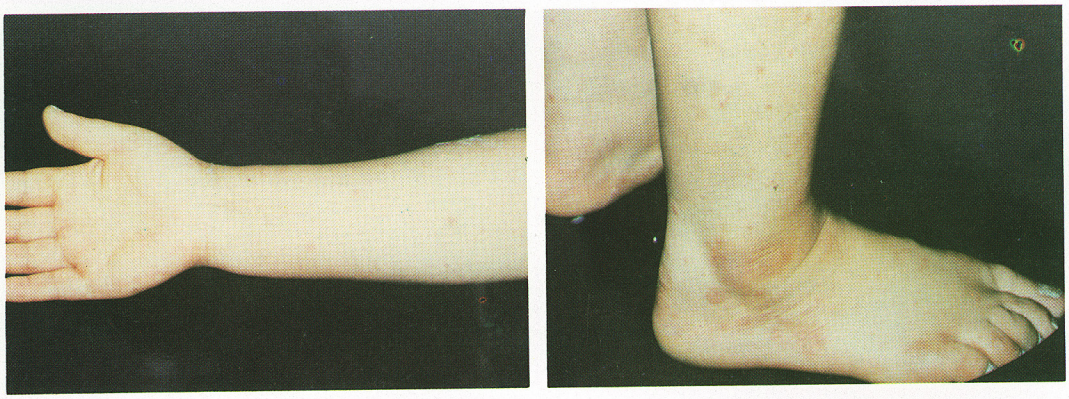

Fig. 1. Gross picture of the patient shows multiple papular rashes and petechiae on the forearm (Top), and lower legs (Bottom).

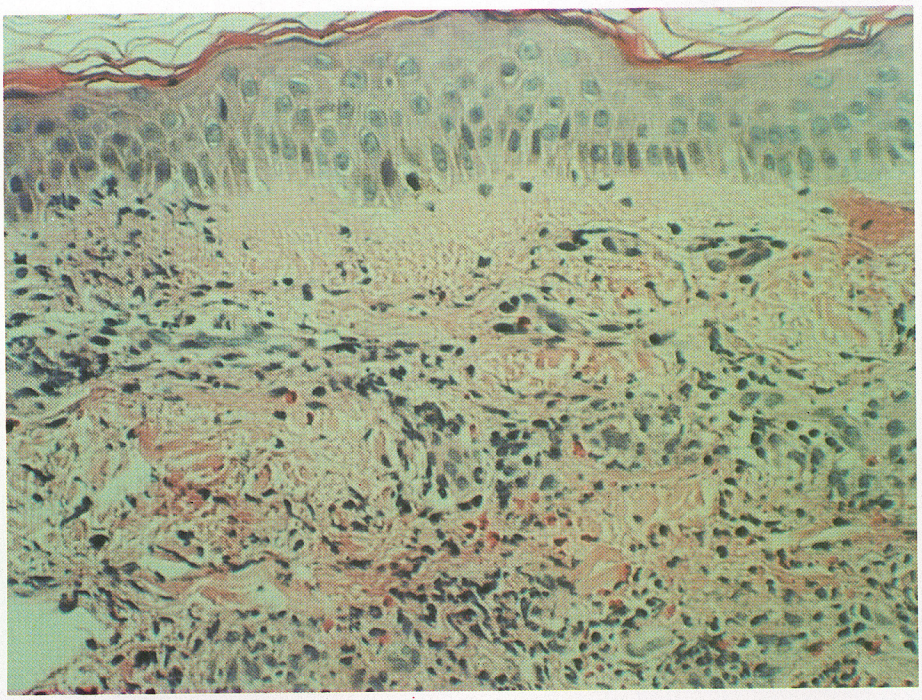

Fig. 2. Photomicrograph of skin shows moderate infiltration of inflammatory cells around the dermal vessels and extravasation of red blood cells in dermis, and relatively intact epidermis (H&E, ×100)

gave a++ test for protein and a+++ test for occult blood; the sediment contained many red cells and 3-6 white cells. The hematocrit was 33.4%; the white-cell count was 10,000, with 85% neutrophil, 10% lymphocyte, 3% monocyte, 1% eosinophil, and 1% basophil. The platelet count was 317,000, the reticulocyte count was 1.4%, the prothrombin time was 11 seconds, with a control of 10.3 seconds. Blood sugar was 92 mg/dl, BUN 13.3 mg/dl, creatinine 1.4 mg/dl, uric acid 4.6 mg/dl, total protein/albumin 6.4/3.3 g/dl, SGOT/SGPT 17/10 unit, alkaline phosphatase 15.2 KA/dl, Na 140 mEq/L, K 3.5 mEq/L, Cl 106 mEq/L, Ca 8.3 mg/dl, phosphorous 3.1 mg/dl, osmolarity 294 mOsm/kg, and LDH 442 unit. It yielded negative tests for LE cell, antinuclear antibody. The cytoplasmic anti-neutrophil cytoplasmic autoantibody was positive by indirect immunofluorescence microscopy with 1:20 titer. C3 was 66.8 mg/dl, C4 30 mg/dl, IgG 1370 mg/dl, IgA 162 mg/dl, and IgM

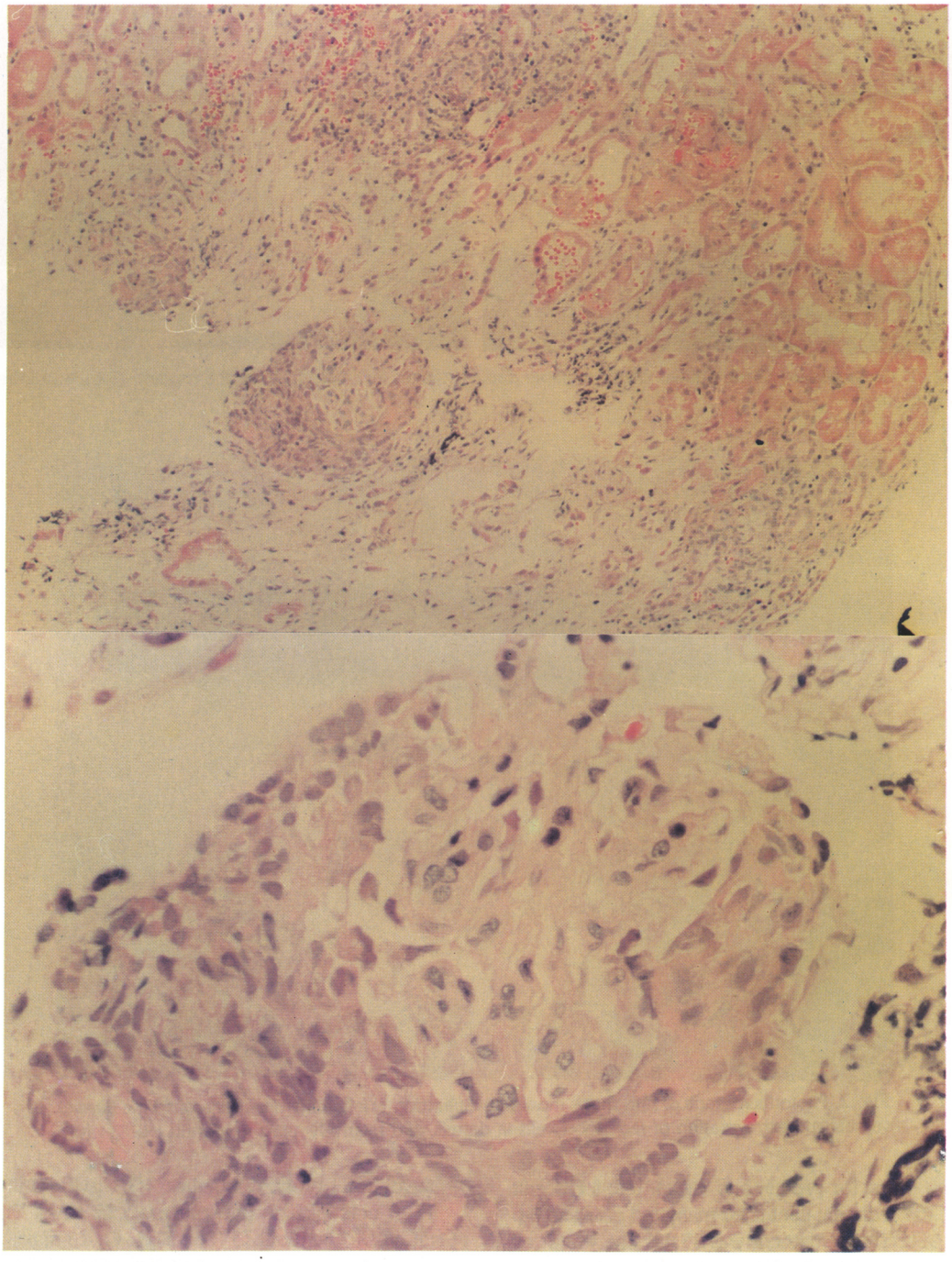

Fig. 3. Phtomicrograph of kidney shows segmental necrosis and crescent formation in the glomeruli. There is moderate infiltration of chronic inflammatory cells in interstitium associated tubular atrophies (Top: H&E, ×100). The glomerular tuft is compressed by cellular crescent that occupies 80% of the circumference of Bowman's capsule (Bottom: H&E, ×400).

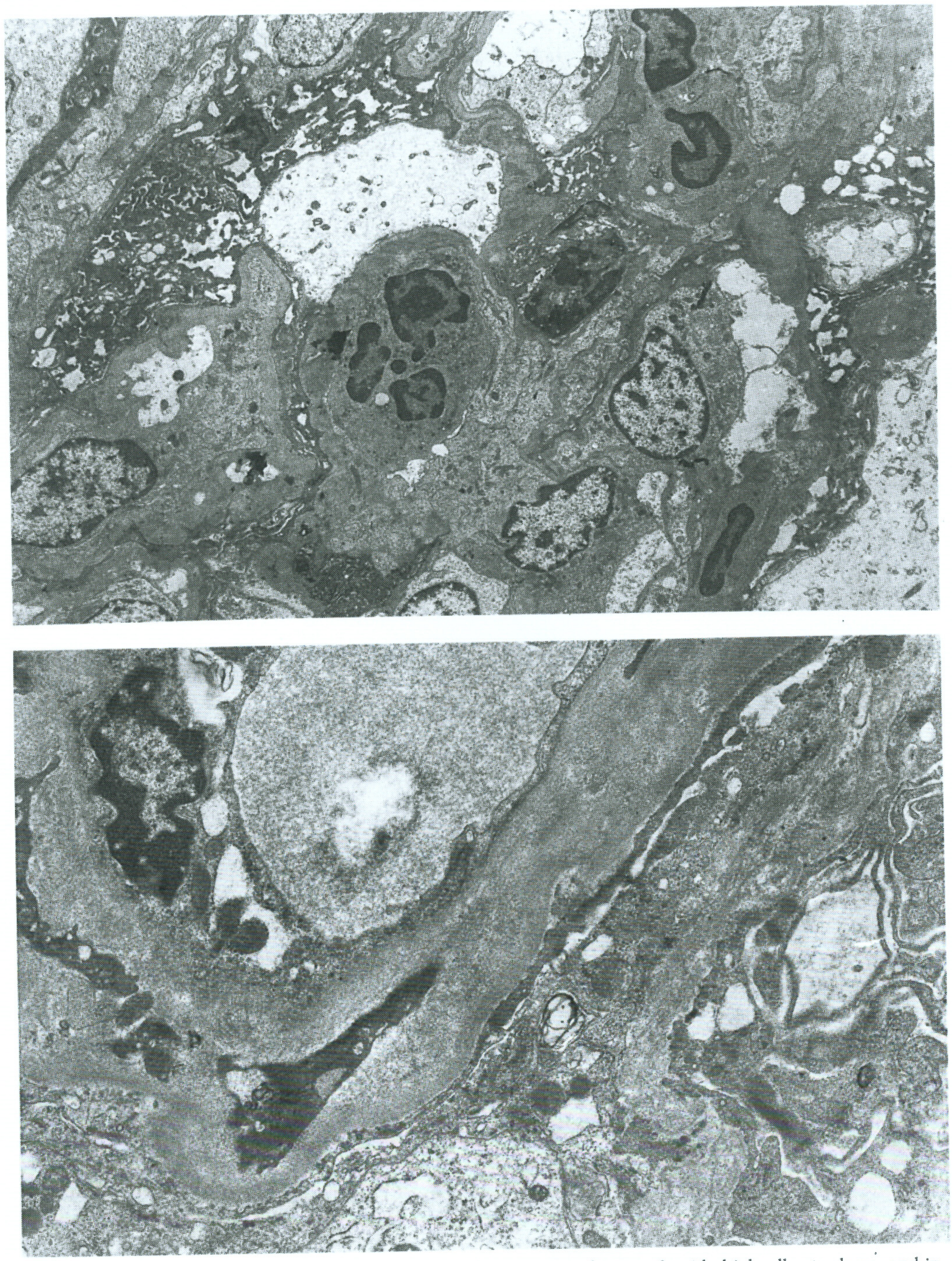

Fig. 4. Electron microscopy of kidney shows edema, degenerative change of epithelrial cell cytoplasm, and intraluminal neutrophil infiltration (Top: ×5,000). No immune deposits and partial mesangial interposition in GBM (Bottom: ×12,500).

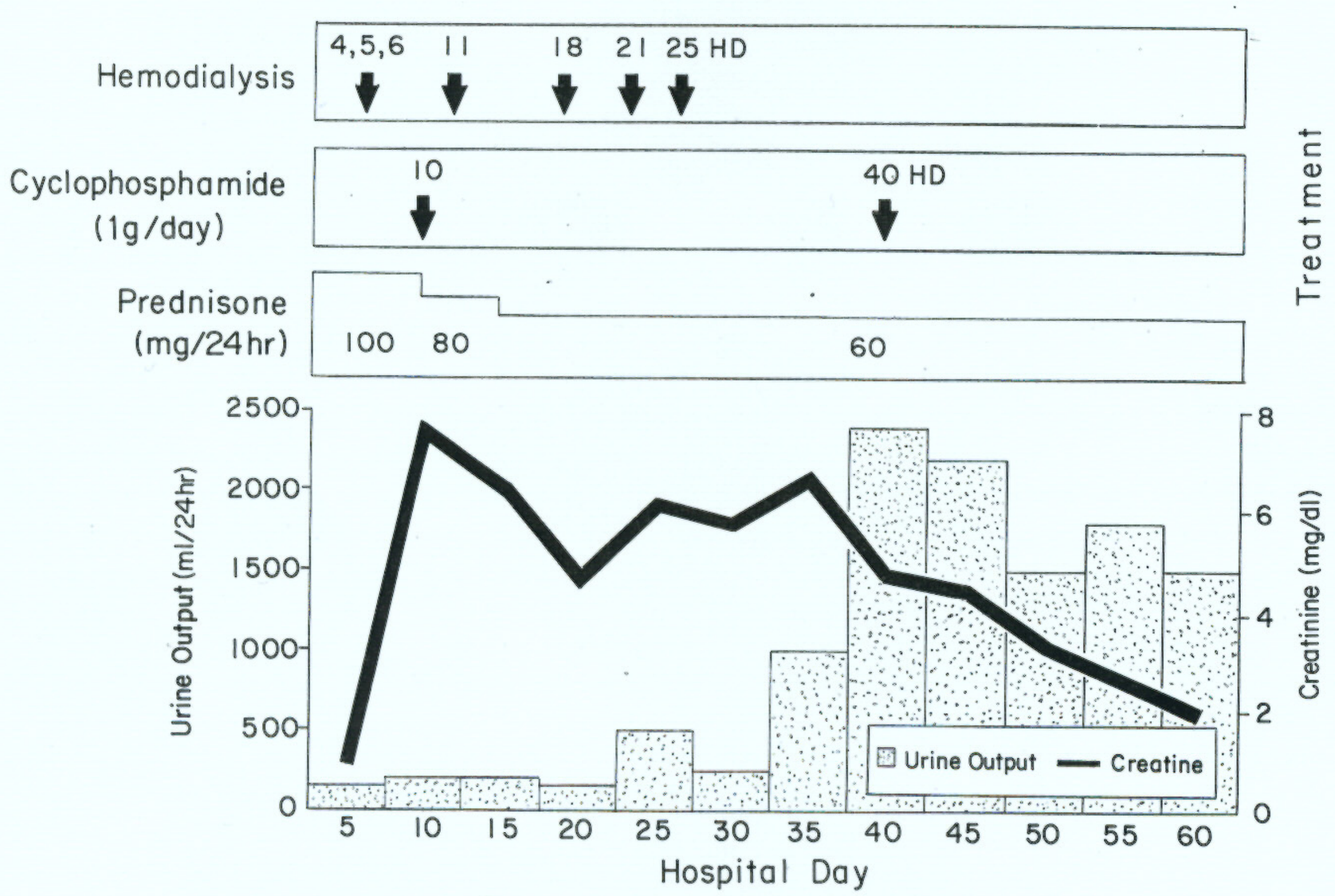

Fig. 5. Changes of urine volume and renal function after hemodialysis and combined immunosuppressive treatment with steroid and monthly intravenous cyclophosphamide therapy in the patient with RPGN.

138 mg/dl. The chest film showed no definite abnormality. Ultrasonographic examination showed both kidneys were normal in size. At the time of admission, three sets of blood culture were drawn, which returned growing no microorganisms. Biopsy of the purpuric skin lesions showed 'leukocytoclastic vasculitis' (Fig. 2). On the third hospital day, she received intravenous pulse methylprednisolone for 3 days and then given maintain oral prednisone while it continued to show an increased serum creatinine concentration (7.6 mg/dl) and oliguria. On the 4th hospital day hemodialysis was started. A renal biopsy was performed on the 7th hospital day and 4 of 10 glomeruli showed accumulation of cells in Bowman's space in the form of crescents, and moderate infiltration of chronic inflammatory cells in the interstitium associated tubular atrophies (Fig. 3). The immunofluorescence microscopy showed no deposits of IgG, IgM, IgA and C3. And the electron microscopy showed no immune deposits (Fig. 4). Then she received a bolus of 1g cyclophosphamide by parenteral route on the 10th hospital day and then monthly. As shown in figure 5, the renal function was rapidly improved. The serum creatinine concentrations were stabilized at a slightly higher value after then, and in August 1991, 2 months after renal biopsy, her serum creatinine was 1.9 mg/dl. The patient's condition was clinically stable for the next 6 months and her serum creatinine was 1.8 mg/dl in November, 1991.

DISCUSSION

RPGN is a heterogeneous disease entity and can be divided further on immunopathogenetic criteria into subgroups with different prognoses and responses to treatment (Atkins, 1988). By immunofluorescence microscopy, one group has anti-GBM antibody deposition (anti-GBM glomerulonephritis) and the other group has a spectrum of immunoglobulins and complements deposition.

The presence or absence of a systemic illness further characterizes those patients without anti-GBM antibody. In a Mayo Clinic study of 64 crescentic glomerulonephritis patients, 23% had anti-GBM antibody deposition, 26% had idiopathic crescentic glomerulonephritis without a systemic illness, and 51% had crescentic glomerulonephritis with a systemic illness consistent with vasculitis (Zashin, 1990). Of those patients with a systemic illness, slightly more than half (55%) had tissue-proven vasculitis and slightly less than half (45%) had no evidence of vasculitis (Velosa, 1987). In vasculitides the kidney is frequently affected, but patients with renal vasculitis present a different clinical feature. Renal vasculitis can be manifested as a part of systemic vasculitis at the onset or later in the course of the disease (Serra, 1984). In this case, the patient had clinical manifestations of systemic vasculitis such

as malaise, arthralgia, myalgia, and purpuric skin lesions, and pathologically she had 'leukocytoclastic vasculitis' in the skin biopsy, necrotizing inflammation in the renal biopsy, and the paucity of immune depositions in the immunofluorescence and electromicroscopic study of the renal biopsy.

Approximately 80% of patients with pauci-immune glomerulonephritis have antineutrophil cytoplasmic autoantibodies (ANCAs) in their circulation (Jennette, 1990). ANCAs are a useful serologic marker and may be involved in the pathogenesis of the most common types of crescentic glomerulonephritis and systemic vasculitis (Glassock, 1991). By indirect immunofluorecence microscopy using alcohol-fixed neutrophil as substrate, ANCAs can be categorized into two major types, C-ANCA with cytoplasmic staining, and P-ANCA with artificial perinuclear staining. The different types of ANCAs have different specificities, and ANCA-associated diseases for a continuum from renal-limited disease to widespread systemic vasculitis (Jennette, 1990). It was positive test for C-ANCA in this case.

The treatment of RPGN can be divided into two major categories: (1) management of the uremia, (2) immunosuppressive treatment to arrest the immunologic injury to the kidney (Jennette, 1990). The adequate control of blood pressure and volume expansion is mandatory and prompt dialysis may be required if the manifestation of uremia is severe enough. Combined immunosuppressive treatment with cytotoxic agents and steroids can be used to ameliorate the immunologic injury of salvageable glomeruli. Plasmapheresis is also worthy of consideration to reduce the circulating inflammatory mediators.

In general, untreated patients with RPGN almost always experience deterioration to the point of end stage of renal disease (Tuma, 1976; Velosa, 1987). In a single center, 48 patients with RPGN who were treated by immunosuppressive treatment, renal function was not recovered in any of the 21 patients with anti-GBM antibody mediated disease, while it was recovered in 63% of patients without these autoantibodies (Glockner, 1988; Hind, 1983). Current approach to treatment in patients with oliguria and pronounced loss of renal function would be methylprednisolone pulse therapy. Plasmapheresis combined with immunosuppressive drug therapy may be required in those who do not respond to conventional methylprednisolone pulse therapy (Fauci, 1979; Adler, 1981; Bruns, 1989).

The presence of oliguria and pronounced loss of renal function are two important variables that are associated with a poor outcome of renal function and increased mortality (Hind, 1983; Serra, 1984; Velosa, 1987; Keller, 1989). But there was no correlation between the extent of crescent formation and the recovery rate of renal function in those patients without circulating anti-GBM antibodies in a single center study (Hind, 1983). Despite the presence of oliguria and rapidly progressive deterioration of renal function, this case showed a favorable response to treatment with hemodialysis and combined immunosuppresive treatment with steroids and monthly intravenous cyclophosphamide therapy.

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