Case Report
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Wegener's Granulomatosis Vasculitis and Granuloma: A Case Report

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Abstract
A 13-year-old girl was admitted to our hospital because of fatigue, oliguria, and edema of lower extremities. Her laboratory workup showed an acute renal failure (BUN= 225 mg/dl, Creatinine= 13.25 mg/dl). She also had a massive proteinuria.
A renal biopsy showed cellular crescentic glomerulonephritis and positive C-ANCA. The serum Creatinine level decreased after dialysis and treatment with high-dose methylprednisolone, rituximab and plasmapheresis. She did not require dialysis after discharge from the hospital. This is a report of a rare case of GPA presenting with 100% cellular crescentic glomerulonephritis.

Keywords: Pauci-Immune Necrotizing Glomerulonephritis; Crescentic Glomerulonephritis; Wegener's Granulomatosis; Child.

Conflict of interest: The authors declare no conflict of interest.
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Introduction
Pauci-immune necrotizing and crescentic glomerulonephritis (GN) refers to a necrotizing GN in which there are few or no immune deposits seen by immunofluorescence or electron microscopy. Most of the patients with limited renal vasculitis are positive for ANCA, and the systemic symptoms of granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA) are present in most of them (1,2). Renal-limited vasculitis refers to pauci-immune crescentic GN limited to the kidney. ANCA-negative pauci-immune crescentic GN and renal-limited vasculitis may be similar to GPA and MPA in systematic symptoms, renal biopsy findings, and prognosis. However, ANCA-negative pauci-immune crescentic GN may be the result of abnormalities of the alternative pathway of complement, as shown in one study (3).

Abbreviations of the study

ACR	American College of Rheumatology
ANCA	Antinuclear (Antineutrophil) cytoplasmic antibodies
GBM	Glomerular basement membrane
GN	Glomerulonephritis
GPA	Granulomatosis with polyangiitis (Wegener's)
MPA	Microscopic polyangiitis
MPO	Anti-myeloperoxidase
PR3	Anti-proteinase-3
RPGN	Rapidly progressive glomerulonephritis

Case report
The patient was a healthy-looking 13-year-old girl presenting to the emergency department with symptoms of fatigue, oliguria, and edema of the lower extremities. She had acute renal failure (BUN=225 mg/dL, Cr= 13.25 mg/dL, and K= 7.6 mEq/L). Urinalysis showed massive hematuria and proteinuria (>300 mg/dL). A renal ultrasound was done immediately. Her symptoms started two months earlier with a common cold and otitis media. A pediatric allergist and a pediatric rheumatologist diagnosed her as a probable case of Wegener's granulomatosis (GPA) considering the laboratory findings, including a positive C-ANCA and negative PR3 and MPO as well as radiological

findings such as brain and sinus MRI. She had no family history of renal disease and did not smoke, drink alcohol, or use illicit drugs. One week after presentation, further analysis showed that her serological tests were positive for antinuclear antibody, antinuclear cytoplasmic antibody (ANCA), and C3. A renal biopsy was performed, which showed 100% cellular crescentic glomerulonephritis (Figure 1) and positive C-ANCA (Figure 2), crescentic glomerulonephritis. Detailed work-up revealed no evidence of pulmonary or other systemic features. The patient was diagnosed with pauci-immune glomerulonephritis (GN) and was treated aggressively with immunosuppressive therapy.

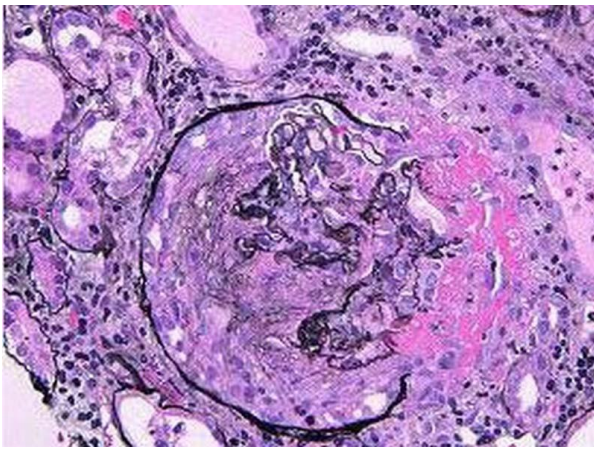

Figure 1. Crescentic glomerulonephritis

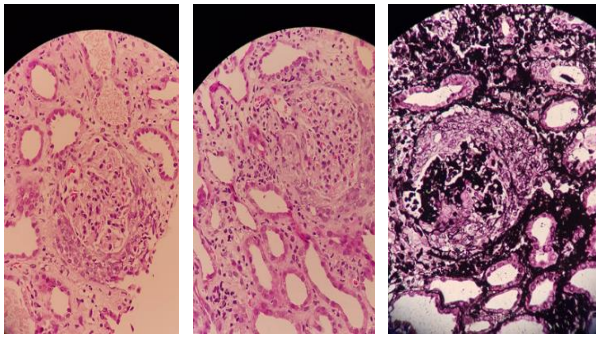

Figure 2. Positive C-ANCA crescentic GN

Discussion

Small scattered immune deposits in the mesangium and glomerular capillary wall may be seen in some patients with pauci-immune crescentic GN. This finding does not exclude a diagnosis of pauci-immune crescentic GN in the appropriate clinical settings with a positive ANCA.

The American College of Rheumatology (ACR) suggested four criteria to diagnose GPA, and a patient with two or more of the following symptoms is a probable case of GPA. These criteria include nasal/oral inflammation, abnormal chest radiograph, abnormal urinary sediment, and pathologic correlation (4). ACR did not provide specific criteria for MPA; these criteria do not differentiate GPA from either MPA or non-vasculitic diseases that can mimic GPA.

The presenting complaints in rapidly progressive glomerulonephritis (RPGN) with crescentic GN may be similar to severe postinfectious glomerulonephritis that presents with a severe nephritic syndrome, including an acute onset of macroscopic hematuria, decreased urine output, hypertension, and edema. More commonly, however, the initial symptom of RPGN is fatigue or edema (5).

Nearly all cases have renal insufficiency at diagnosis, with the plasma creatinine concentration often over 3 mg/dL (264 micromole/L). Dysmorphic hematuria, red cell and other casts, and a variable degree of proteinuria are typically seen in urinalysis. Glomerular filtration rate usually reduces markedly, resulting in limiting the rate of protein filtration; therefore, nephrotic syndrome is not common and often occurs in patients with less severe renal failure (6). Hematuria is very common (7). The cause of hematuria is not well understood, but the absence of hematuria is explained in other types of GN such as membranous nephropathy. Hypertension is not common and is usually mild if present.

Diagnosis should be done urgently and accurately for a patient who has clinical symptoms suggesting RPGN. If pauci-immune crescentic GN is likely, appropriate serologic tests should be performed including ANCA, anti-GBM antibodies, complement component assays, antinuclear antibodies, and cryoglobulins, according to the history, examination, and biopsy findings.

Most of the patients with RPGN are initially treated with pulse methylprednisolone, followed by daily oral prednisone, oral or intravenous cyclophosphamide or rituximab, and plasmapheresis per case. Early diagnosis, according to kidney biopsy and serologic testing, and early initiation of appropriate therapy should be

considered to minimize the degree of irreversible renal injury.

Our patient underwent dialysis initially due to a high creatinine level; then, methylprednisolone, plasmapheresis, cyclophosphamide and rituximab were administered according pathologic findings.

Two randomized trials have shown that rituximab is an effective alternative to cyclophosphamide for the initial treatment of new-case patients or relapsing cases that previously received cyclophosphamide or other immunosuppressive therapies (8, 9). However, in one of two studies, patients in the group that received rituximab also received cyclophosphamide. The rate of serious adverse effects was similar for both drugs.

The RAVE trial was a randomized placebo-controlled multicenter non-inferiority trial that compared induction therapy with rituximab (375 mg/m^2/week for four weeks) and oral cyclophosphamide (2 mg/kg/day) in 197 patients with GPA or MPA (75% of the patients had GPA and 25% had MPA); moreover, 49% of the patients were new cases while 51% were relapsing cases (8). All of the patients were received one to three doses of pulse methylprednisolone (1000 mg) followed by oral prednisone (1 mg/kg/day). Rituximab was not significantly different from cyclophosphamide in inducing remission at six months (64% versus 53%) in new cases. However, considering inducing remission at six months in the 100 relapsing cases, rituximab was significantly different from cyclophosphamide (67% versus 42%). No difference was reported in the number of adverse effects between the two groups.

After 18 months follow-up of 197 patients who initially participated in the RAVE study, complete remission was seen in 146 patients (10). In this trial, one group only received rituximab, while cyclophosphamide was switched to azathioprine in the other group within the first six months. At 18 months, the rate of staying in complete remission was not significantly different between rituximab- and cyclophosphamide-based induction (39% versus 33%). In addition, the number of deaths or the rate of severe infections was similar in two groups.

Conclusion

Based on kidney biopsy, RPGN requires an aggressive therapy, including plasmapheresis and pulse methylprednisolone, rituximab, and cyclophosphamide. If rapid and timely treatment is not done, the risk of disease progress and irreversible damage is high; therefore, aggressive treatment is advised.

Conflict of Interest

The authors declare no conflicts of interest.

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