Case Report
http://journals.sbmu.ac.ir/jpn
https://doi.org/10.22037/jpn.v9i3.33164

Delayed Diagnosis of Proteinase 3- Anti-Neutrophil Cytoplasmic Antibody Associated Vasculitis, A Case Report and Review of Literature

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Received: December, 2021
Revised: July, 2021
Accepted: September, 2021

Abstract
Anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis is a type of systemic autoimmune disease with blood vessels swelling and inflammation. Wegener's Granulomatosis (WG) is closely associated with antineutrophil cytoplasmic autoantibodies, particularly those directed to proteinase 3 (PR3). An 18-year-old boy with granulomatosis with polyangiitis (GPA) who was diagnosed 6 months back with scleritis and sinusitis at the onset of the disease. During his initial visits to Ear Nose Throat and ophthalmology departments lab tests was not performed on time due to lack of typical symptoms of kidney involvement. Half a year later, lab tests showed PR3-ANCA (Proteinase 3) positive and advanced renal dysfunction, and was finally diagnosed as sclerotic renal failure with fibrotic crescents based on renal biopsy. Scleritis may be the earliest manifestation in systemic vasculitis and is sometimes hard to diagnose at the onset. Delayed diagnosis and treatment will lead to irreversible renal dysfunction.

Keywords: Vasculitis; ANCA; Granulomatosis with Polyangiitis; GPA; Scleritis; Delayed Diagnosis; Sclerotic Glomerulonephritis.

Conflict of interest: The authors declare no conflict of interest.
Please cite this article as: Sampathkumar G, Yu Y, Wen A, Zhang Y. Delayed Diagnosis of Proteinase 3- Anti-Neutrophil Cytoplasmic Antibody Associated Vasculitis, A Case Report and Review of Literature. J Ped Nephrol 2021;9(4):1-3.
https://doi.org/10.22037/jpn.v9i3.33164

Introduction
The antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a rare autoimmune disease of unknown cause, characterized by inflammatory cell infiltration causing necrosis of blood vessels (1). Wegener's Granulomatosis (WG) is closely associated with ANCA, particularly those directed to proteinase 3 (PR3) (2). Both principally associated with antibodies to myeloperoxidase (MPO-ANCA) (3). Renal vasculitis is the most common severe manifestation of ANCA-associated vasculitis (AAV) progressing to glomerulonephritis (GN) (4). Glomerulonephritis in relation to MPA has more characteristics of chronic injury at the time of presentation than glomerulonephritis in relation to WG, which suggests that the pathogenesis of renal disease in these ANCA subsets could be different (5). The present study reported about an 18-year-old boy who had granulomatosis with polyangiitis (GPA) and scleritis initially had developed sclerotic glomerulonephritis.

Case report
An 18-year-old male presented with facial edema, occasional cough, breathlessness on exertion for more than a month and foamy urine. He consulted ophthalmology and ENT department at the affiliated hospital of Nantong university where he was diagnosed with scleritis and sinusitis. On physical examination height and weight were 168 cm and 58.4 kg respectively. His body temperature (36.5℃), blood pressure (145/92mmHg) and pulse (97/min)

were recorded. Cardiovascular, respiratory, and central nervous systems were normal.

The patient had decreased urinary output and loss of appetite. Blood tests showed WBC 8.9×10^9, RBC 2.57×12^9, Hb 75 g/L, Plt 170×10^9 and ESR 87 mm/hr. Liver function results were ALT 25 u/L, AST 30 u/L, Alb 34.2 g/L, Globulin 25.6 g/L. Renal function test were BUN 50.9 mmol/L, SCr 1781 u mol/L, cystatin C 4 mg/L.

Preliminary diagnosis was done as stage 5 chronic kidney disease (CKD) with pulmonary infection. The initial treatments included intermittent hemodialysis by temporary femoral vein catheter insertion, cefoperazone for antibiotic treatment, erythropoietin for anemia, and PPI for gastric protection.

Dipstick urinalysis report was protein 3+, RBC 6/HP, WBC 3/HP and 24-hour total protein was 0.98 g/d (total urinary output volume was 300 ml), renal function reported BUN 52 mmol/L, Scr 1474 u mol/L, Ccr 0.9 ml/min, electrolyte were K^+ 7.2 mmol/L, P^{3+} 3.14 mmol/L, Ca^{2+} 1.34 mmol/L, Co2cp 12.2 mmol/L, liver function: ALT 28 U/L, AST 30 U/L, Alb 34.2 g/L, Glb 25.6 g/L, iPTH 313.8 pg/ml, Anti-HCV(-), Anti-HIV(-), Anti-TP(-), HBsAg(-), ESR 45 mm/h, MPO-ANCA(-), Anti-GBM(-), PR3-ANCA 170 AU/ml(normal≤120).

The second titer of PR3-ANCA was found 210 AU/ml.

Ultrasound of kidney showed that bilateral kidney size were 104×43×42 mm, 110×52×52 mm, respectively (figure 1 a), cytological examination of the bone marrow revealed poor hyperplasia of the red cell line (figure 1b), pulmonary CT scan showed scattered inflammation in bilateral lungs, increased density shadow in right lower lung (figure 1c), and paranasal sinus CT scan showed bilateral maxillary sinusitis, ethmoidal sinusitis and sphenoid sinusitis, nasal septum deviation (figure 1d).

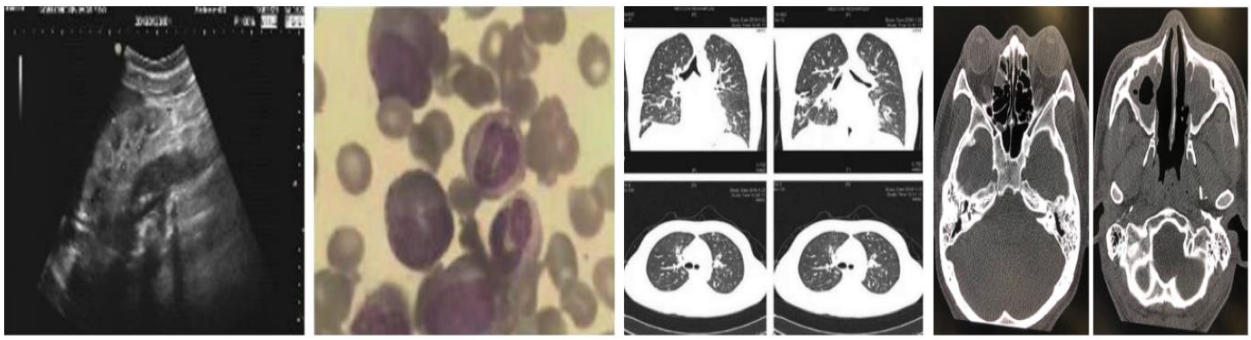

Fig 1a. Ultrasound. Fig 1b: Bone marrow smear Fig 1c: Pulmonary CT scan Fig 1d: Paranasal sinus CT scan

Figure 1. Ultrasound of kidney and cytological examination of bone marrow

After the clinical diagnosis of AAV, corticosteroid (MP 250mg/d) and plasma exchange were conducted immediately. The final diagnosis was AAV, stage 5 chronic kidney disease.

Light microscopy (Figure 2) showed all 22 glomeruli were obsolete because of sclerosis with fibrotic crescentic remnant. Severe chronic tubulointerstitial lesions with tubular atrophy and basement membrane thickening (60%) was noted. Diffuse macrophage infiltrated in the fibrotic interstitial area. (PAS, MASSON, ×400. PASM, ×200) c. Results of Microscopic polyangiitis and Wegner's values among different organ systems are presented in (Table 1).

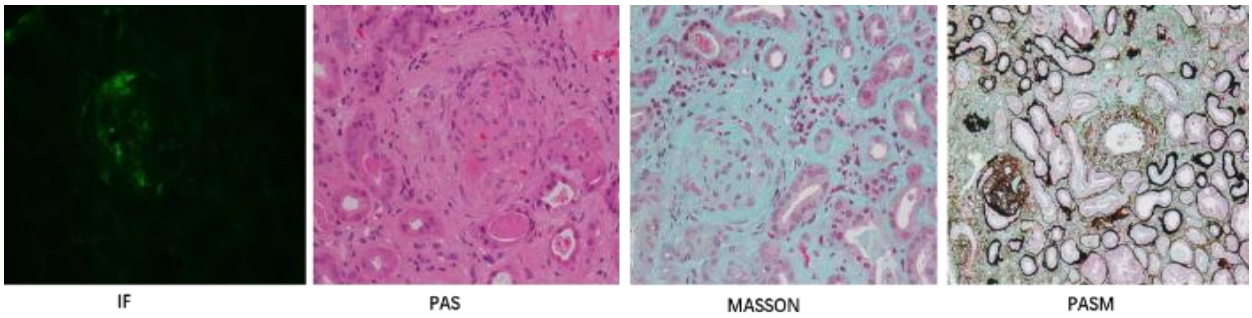

Figure 2. Immunofluorescence showing compliment C3 positive, IgG, IgA, IgM and C1q were all negative (IF, ×400)

Table 1. Microscopic polyangitis and Wegner's values among different organ systems

Organ system	Microscopic polyangitis	GPA(Wegner's)
Kidney	90	80
Skin/Cutaneous	40	40
Lungs	50	90
Ear, Nose, Throat	35	90
Musculoskeletal	60	60
Neurologic	30	50
Gastrointestinal	50	50

Discussion

In this case, 18 years old boy presented with facial edema with foamy urine. While reviewing his past history it is seen that he had visited ENT, Respiratory and ophthalmology departments for the past 6 months. But attention was not paid by the consulting doctors to the potential systemic disease with respiratory tract involvement. GPA is the most common cause of ENT and ocular involvement in patients with systemic vasculitides (6). Further studies on the role of these autoantibodies are required to better categorize and manage appropriately the patients with small vessel vasculitis and to develop more targeted therapy (7). Patients with AAV exhibit higher rates of malignancy (8) and the potential secondary etiologies for AAV should be considered. Hence this case report suggests that in every hospital MDT principle should be carried out, especially among patients with systemic diseases with isolated organ involvement or atypical presentation to make correct diagnosis at the onset without delay.

Conclusion

Scleritis may be the earliest manifestation in systemic vasculitis and is sometimes hard to diagnose at the onset. Delayed diagnosis and treatment will lead to irreversible renal dysfunction.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Acknowledgements

We acknowledge the technical support in data entry, analysis and manuscript editing by "Evidencian Research Associates"

Financial support and sponsorship

The project was self-funded. No external agency had funded the project.

Conflicts of interest

The authors declare no conflicts of interest.

Author Contributions

Sampathkumar Gopika, Yamin Yu, Ailing Wen contributed to patient care Sampathkumar Gopika, Yamin Yu, Yide Zhang contributed to the writing of the manuscript. Ailing Wen, Yide Zhang contributed to the editing of the manuscript. Sampathkumar Gopika, Yamin Yu, Ailing Wen, Yide Zhang reviewed and amended subsequent drafts and approved the final version.

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