*Case Report*

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# Multiple renal infarctions in a patient caused by granulomatosis with polyangiitis

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**Abstract**

Granulomatosis with polyangiitis (GPA) is a small-vessel vasculitis that is highly associated with anti-neutrophil cytoplasmic antibodies. GPA carries an increased risk of organ infarction, but renal infarction is rare. We herein describe a case of multiple renal infarctions caused by GPA. A 66-year-old man presented with hearing loss, nasal discharge, fatigue, and weight loss for several months. Cross-sectional contrast-enhanced computed tomography images revealed multiple low-attenuation areas in both kidneys. He subsequently developed fever and impaired renal function. Blood serum was positive for cytoplasmic anti-neutrophil cytoplasmic antibody and a renal biopsy showed granulomatous necrotizing vasculitis. He was diagnosed with GPA and treated with high-dose corticosteroids, plasma exchange, and cyclophosphamide. The patient ultimately entered clinical remission.

**Keywords**

Granulomatosis with polyangiitis, renal infarction, anti-neutrophil cytoplasmic antibody, renal function, necrotizing vasculitis, computed tomography

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## Introduction

Granulomatosis with polyangiitis (GPA, formerly known as Wegener's granulomatosis) is a necrotizing granulomatous vasculitis involving capillaries, venules, arterioles, and arteries throughout the body, with the upper and lower respiratory tract and

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kidneys being the most commonly affected. GPA has a peak incidence at 65 to 75 years, but can occur at any age, with a slight male predominance.[1] The etiology of GPA may include infectious, environmental, chemical, toxic, or pharmacological triggers in people who are genetically predisposed to this autoimmune disease.[2] In this study, we report an unusual case of GPA in a patient who presented with multiple renal infarctions and features of medium-vessel vasculitis.

## Case report

A 66-year-old man was admitted to the Department of Otolaryngology in early December 2016 for nasal obstruction and hearing loss. He was considered to have exudative otitis media and sinusitis. He received ear-puncture drainage and anti-infective treatment, which relieved his symptoms; however, the symptoms recurred on four subsequent occasions. Five months later, the patient exhibited gradually worsening bilateral conjunctival redness, but did not seek help for his symptoms. In August 2017, the patient developed increased fatigue and numbness in his lower extremities and lost approximately 25 kg in weight over 10 months. His health deteriorated from being physically active and independent to mostly bedridden. He was therefore hospitalized in the Department of Endocrinology in September 2017. He had a 15-year history of hypertension and diabetes but denied any history of drug abuse and any family history of coagulopathy, connective tissue disease, or renal disease. On admission, the patient's temperature was 36.3°C, his blood pressure was 122/66 mmHg, pulse was 73 beats/minute, and respiratory rate was 16 breaths/minute. He appeared cachectic (body mass index 17.0 $kg/m^2$) with temporal wasting, and looked older than his actual age. He appeared mildly anemic with bilateral conjunctival and corneal redness. Bilateral lung fields were mostly clear. Examination of his heart and abdomen showed no edema in the extremities. Laboratory examinations showed microcytic anemia (hemoglobin 98 g/L) with normal white blood cell ($10.0 \times 10^9$/L) and platelet ($248 \times 10^9$/L) counts. His renal function was normal (serum creatinine (sCr) 94.16 μmol/L) and inflammatory markers were elevated (erythrocyte sedimentation rate (ESR) 74 mm/hour and C-reactive protein (CRP) 124 mg/L). A urine dipstick test revealed moderate proteinuria and hematuria. Coagulation examination showed an elevated D-dimer of 2413 ng/mL, and other coagulation parameters were normal.

The initial diagnosis was possible tuberculosis infection or malignancy. However, screening for serum tumor markers, T cell detection for tuberculosis infection, and tuberculosis antibody tests were negative. Contrast-enhanced computed tomography (CT) of his chest, abdomen, and pelvis revealed multiple low-attenuation areas in both kidneys, multiple enlarged lymph nodes in the retroperitoneum, and pelvic effusion (Figure 1). After 14 days in hospital, the patient developed fever with a maximum body temperature of 38.5°C. Sputum culture showed moderate numbers of Gram-positive cocci and Gram-negative bacilli, and his sCr increased to 137.82 μmol/L. A bone marrow biopsy was performed to exclude lymphoma, but no significant abnormality was found. He was then transferred to our department in October 2017.

We reviewed the relevant results, and his sCr had risen to 314.11 μmol/L. Routine blood tests showed hemoglobin 10.3 g/L with mild thrombocytosis (platelet count $400 \times 10^9$/L), leukocytosis (white cell count $23.91 \times 10^9$/L), and elevated ESR (72 mm/hour) and CRP (139.57 mg/L). Autoimmune serology was positive for cytoplasmic anti-neutrophil cytoplasmic antibody (c-ANCA), with elevated levels

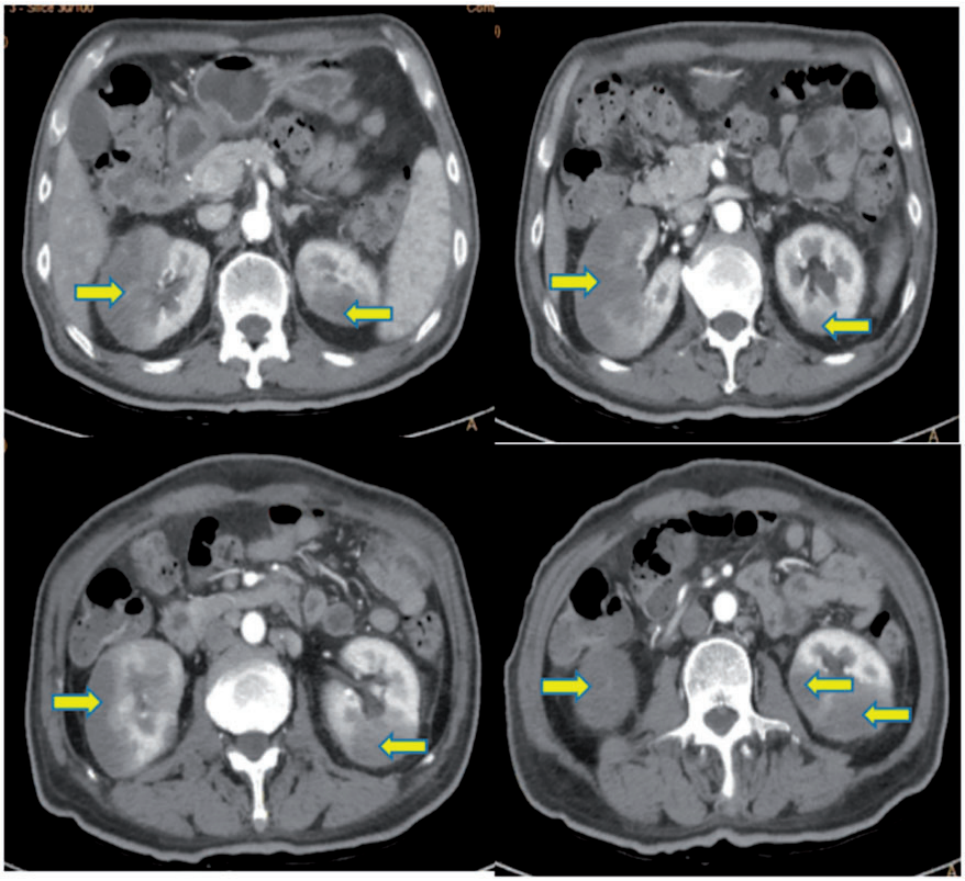

**Figure 1.** Imaging of renal infarcts. Contrast-enhanced CT demonstrating multiple low-attenuation areas in both kidneys (arrows).

of myeloperoxidase (MPO) antibody. Antinuclear antibodies, glomerular basement membrane antibodies, and C3 and C4 levels were normal. Human immunodeficiency virus and hepatitis B and C serology tests were negative. Urine culture for *Mycobacterium tuberculosis* was negative. Urinalysis showed glucose 1+, and no hematuria or proteinuria (Table 1). Percutaneous renal biopsy was performed to identify the cause of the acute kidney injury and multiple low-attenuation areas in the kidneys.

Six cores of renal tissue were examined, one of which was infarcted. The other specimens included 15 glomeruli, with slight diffuse proliferation of mesangial cells and matrix, and vacuolar degeneration of the basement membrane, including the formation of two cellular and two fibrocellular crescents. There was diffuse atrophy, lack of renal tubules, and renal interstitial infiltration of diffuse lymphocytes and monocytes, plasma cells, and a few eosinophils with fibrosis, mostly granulomatous in structure. The arteriole wall was thickened, the segmenting arteriole wall was infiltrated by neutrophils, and a segmenting thrombus had formed. Immunofluorescent studies showed no

**Table 1.** Laboratory data.

| Variable | On admission | Transferred to our department |
|---|---|---|
| Routine blood test | | |
| White blood cell ($\times 10^9$/L) | 10.0 | 23.91 |
| Hemoglobin (g/L) | 98 | 103 |
| Platelet ($\times 10^9$/L) | 248 | 400 |
| Serum creatinine (μmol/L) | 94.16 | 314.11 |
| eGFR (mL/min/1.73 $m^2$) | 73.88 | 18.40 |
| Blood urea nitrogen (mmol/L) | 7.44 | 30.31 |
| C-reactive protein (mg/L) | 124 | 139.57 |
| Erythrocyte sedimentation rate (mm/hour) | 74 | 72 |
| Routine urine examination | | |
| Proteinuria | Moderate | Negative |
| Hematuria | Moderate | Negative |
| Coagulation examination | | |
| PT (s) | 13.0 | 12.8 |
| APTT (s) | 29.4 | 27.2 |
| AT-III (%) | 85 | 80 |
| INR | 1.2 | 1.18 |
| TT (s) | 14.6 | 14.0 |
| D-dimer (ng/mL) | 2413 | 1098 |
| Fibrinogen (g/L) | 4.9 | 4.80 |
| Serum albumin (g/L) | 28.29 | 28.96 |
| Tumor marker | | |
| Carcinoembryonic antigen | Negative | |
| Alpha fetoprotein | Negative | |
| Carbohydrate antigen 199 | Negative | |
| Carbohydrate antigen 125 | Negative | |
| Total prostate-specific antigen | Negative | |
| Tuberculosis antibody test | Negative | |
| Immunological assays | | |
| Antinuclear antibody | Negative | Negative |
| Anti-dsDNA | Negative | Negative |
| C3 | | Negative |
| C4 | | Negative |
| Anti-GBM | | Negative |
| c-ANCA | | Positive |
| p-ANCA | | Negative |
| MPO antibody (U/mL) | | 310.755 |
| PR3 antibody (U/mL) | | 6.436 |

eGFR, estimated glomerular filtration rate; PT, prothrombin time; APTT, activated partial prothrombin time; AT-III, activated partial prothrombin time; INR, international normalized ratio; TT, thrombin time; c-ANCA, cytoplasmic anti-neutrophil cytoplasmic antibody; p-ANCA, perinuclear anti-neutrophil cytoplasmic antibody; C3, complement C3; C4, complement C4; anti-GBM, glomerular basement membrane antibodies; MPO, myeloperoxidase; PR3, proteinase 3.

staining for IgA, IgG, IgM, C1q, C3, or fibrinogen-related antigen. Hepatitis B surface and core antigens were negative. T cells were negative for tuberculosis-related DNA. A diagnosis of granulomatous necrotizing vasculitis was made, involving larger blood vessels and leading to kidney infarction (Figure 2).

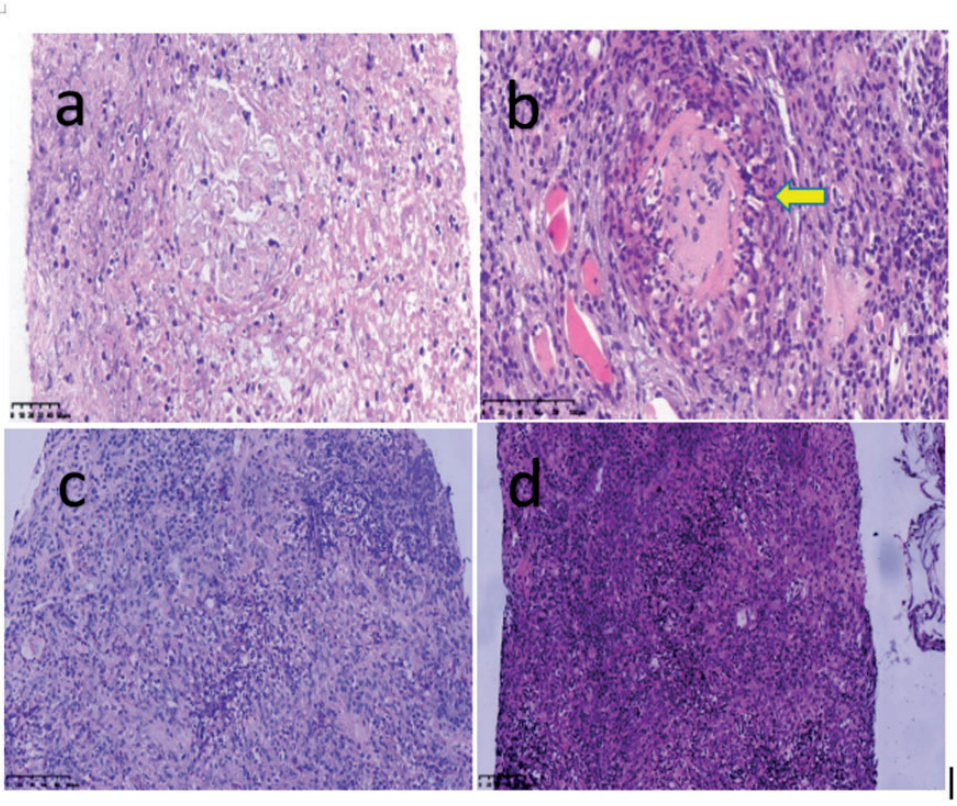


**Figure 2.** Representative images of kidney biopsy sample. (a) Infarcted renal tissue. (b) Arteriole wall infiltrated with neutrophils, and thrombus formation (arrow). (c, d) Interstitial granulomatous lesion. Hematoxylin and eosin staining.

In light of the patient's acute renal failure, he was treated with intravenous methylprednisolone 500 to 1000 mg daily for 3 days followed by oral prednisolone 0.5 mg/kg/day. Plasma exchange was performed seven times to eliminate ANCAs from the peripheral circulation, and pulsed intravenous cyclophosphamide was administered in conjunction with glucocorticosteroids. His renal function gradually recovered, his sCr decreased to 142.95 μmol/L, and his CRP and ESR were normal at discharge. The patient was followed-up as an outpatient in the Nephrology Department and continued to receive daily steroids and monthly intravenous cyclophosphamide. The course of his renal function is summarized in Figure 3.

Ethics approval was not required because the case was reported retrospectively. The patient provided written consent for publication of this report.

## Discussion

GPA is traditionally considered a disease of small-to-medium vessels, with a predilection for renal and pulmonary sites. The diagnostic criteria for GPA include a combination of clinical manifestations of systemic disease that suggest a diagnosis of vasculitis, positive ANCA serology, and

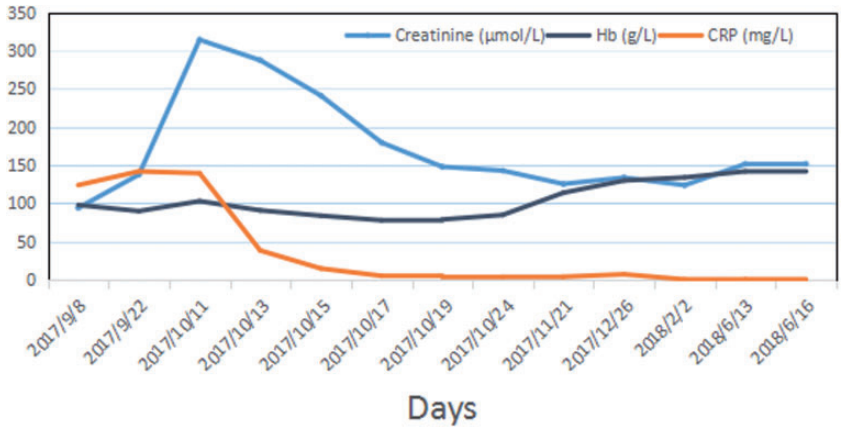


**Figure 3.** Patient's clinical course. Yellow arrow: cytoplasmic-anti-neutrophil cytoplasmic antibody(+), myeloperoxidase 310.755 U/mL; intravenous methylprednisolone 500 to 1000 mg/day for 3 days followed by oral prednisolone 0.5 mg/kg/day; plasma exchange was performed seven times. Blue arrow: intravenous cyclophosphamide 600 mg; oral hormone reduction. Red arrow: intravenous cyclophosphamide 800 mg; oral hormone reduction. Purple arrow: intravenous cyclophosphamide 800 mg; oral hormone reduction. Green arrow: cyclophosphamide total dose 5400 mg; methylprednisolone maintained at 4 mg/day. Hb, hemoglobin; CRP, C-reactive protein.

histological evidence of necrotizing granulomatous inflammation. The immunopathogenesis of GPA is complex and involves the generation of ANCAs against proteinase 3 in approximately 80% and against MPO in approximately 10% of GPA patients.[3] The current patient manifested general malaise, anorexia, weight loss, and pyrexia. He also had high levels of inflammatory indicators and multisystem involvement, including the ear (hearing loss), nose (persistent and recurrent nasal discharge), eyes (scleritis and conjunctivitis), peripheral nervous system (peripheral neuropathy), and kidney (kidney injury). The immunological results were positive for cytoplasmic ANCA with elevated levels of MPO antibodies, and renal puncture pathology showed the formation of renal interstitial granuloma and necrotizing vasculitis.

Imaging results in patients with ANCA-related vasculitis with multiple low-density lesions in both kidneys are rare. Notably, the current patient's renal function was normal when he underwent contrast-enhanced CT, but a possible effect of the contrast agent should be considered, and ultrasound or scintigraphy could be used instead to avoid the risk of contrast-induced nephropathy.

Renal infarction is a necrotizing kidney disease caused by complete interruption of blood flow due to embolization or thrombosis of the main or a branch of the renal artery. The potential causes include blood vessel injury, low-flow states, thrombotic microangiopathy, malignant hypertension, and hypercoagulable states, as seen in patients with a long history of oral contraceptive use or genetic thrombophilic conditions.[4] A large study conducted in Turkey showed that 21.5% of patients with renal infarction had bilateral renal infarctions, and cardioembolic disease was the most common cause.[5] Inflammation-induced thrombosis can also occur in systemic vasculitides, such as aortitis, polyarteritis nodosa, Behçet's disease, and ANCA-associated vasculitis, especially during

active disease. Kang et al.[6] found a high incidence of arterial thrombosis (defined as acute coronary events and ischemic stroke) of 2.67 per 100 person-years in a UK population of patients with ANCA-related vasculitis, particularly in the first year after diagnosis. Although an increased frequency of arterial events, especially cardiovascular events, has been reported in ANCA-associated vasculitis in recent studies, peripheral and abdominal arterial thromboses are less well described.[7–9] The mechanism is presumed to relate to the interaction between neutrophils (activated by tumor necrosis factor-$\alpha$ and ANCA) and endothelial cells, resulting in massive oxidative stress and finally leading to thrombosis and downstream infarction.[10] Renal infarction is rare and often asymptomatic in ANCA-associated vasculitis; however, adequate attention should be paid to this possible diagnosis because of the huge impact of renal cortex infarction on renal function.[11,12] The prognosis may be worse in patients with bilateral infarctions.[13] Information on the use of anticoagulant and/or antiplatelet therapy in ANCA-associated vasculitis is lacking, because of potential hemorrhagic complications. However, Ito et al.[14] reported a case in which intracerebral hemorrhage was caused by ruptured necrotizing angiitis. Aggressive anti-inflammatory treatment during active disease could possibly reduce the risk of thrombotic events.

The current study was limited by the relatively short follow-up time of the patient after discharge, which was not long enough to allow the continued observation of changes in renal function.

In conclusion, the possibility of GPA should be considered when imaging studies reveal multiple low-density foci in the kidney. Early recognition and prompt management can help to reduce the mortality associated with this condition.

## Declaration of conflicting interest

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