Case Report

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
48(10) 1–11

DOI: 10.1177/0300060520963990
journals.sagepub.com/home/imr
SAGE

Antineutrophil cytoplasmic antibody-positive infective endocarditis complicated by acute kidney injury: a case report and literature review

Wei Zhang[1], Hui Zhang[1], Daoxu Wu[2], Haiyang Fu[3], Weiping Shi[3] and Feng Xue[4]

Abstract

Patients with infective endocarditis (IE) may present with multisystem disturbances resembling autoimmune diseases, such as antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). The kidneys are susceptible to damage in IE and AAV, which is a source of diagnostic ambiguity. Therefore, distinguishing infection from an inflammatory process is pivotal for guiding appropriate therapy. We report a 22-year-old man with IE characterized by ANCA positivity and complicated by acute kidney injury. A renal biopsy showed crescentic nephritis with tubulointerstitial lesions. However, transthoracic echocardiography and blood culture provided evidence of IE, and AAV was ruled out. Surgical intervention and antibiotic treatments were successful. We summarized previously reported cases of ANCA-positive IE that had renal biopsy data. We found that ANCA-positive IE can involve multiple organs. The representative renal pathology was crescentic nephritis, focal segmental glomerulonephritis, mesangial cell proliferation, tubular injury, and interstitial oedema. Immunofluorescence showed predominate C3 deposits. Electron microscopy showed electron-dense deposits in the subendothelial or mesangial areas. Eight patients received immunosuppressive therapy with excellent results. Repeated testing for bacterial pathogens and multiple renal biopsies may be useful for diagnosing ANCA-positive IE. With ANCA-positive IE, immunosuppressive therapy along with antibiotic treatments may be beneficial for recovery of renal function.

[1]Department of Nephrology, The Affiliated Hospital of Qingdao University, Qingdao, Shandong, China
[2]Department of Nephrology, Yuhuangding Hospital Affiliated to Qingdao University, Yantai, Shandong, China
[3]Department of Pathology, The Affiliated Hospital of Qingdao University, Qingdao, Shandong, China
[4]Department of Anesthesiology, The Affiliated Hospital of Qingdao University, Qingdao, Shandong, China

Corresponding author:
Feng Xue, Department of Anesthesiology, The Affiliated Hospital of Qingdao University, No. 16 Jiangsu Road, Qingdao 266000, Shandong, China.
Email: xfwwww@163.com

Keywords
Infective endocarditis, antineutrophil cytoplasmic antibody, acute kidney injury, glomerulonephritis, vasculitis, antibiotics, complement 3

Date received: 20 February 2020; accepted: 10 September 2020

Introduction

Antineutrophil cytoplasmic antibody (ANCA) directed against proteinase-3 (PR3) or myeloperoxidase (MPO) is an important diagnostic marker of ANCA-associated vasculitis (AAV).[1] However, ANCA has been detected in 18% to 33% of patients with infective endocarditis (IE).[2] Notably, the kidneys are susceptible to AAV and IE,[1,3] which may lead to misdiagnosis and inappropriate treatment. Therefore, distinguishing infection from an inflammatory process is pivotal for guiding appropriate therapy. ANCA-positive IE complicated by kidney injury is rare, and only 26 cases have been reported.[4–28] Little is known about the associated renal pathology, the use of immunosuppressants, and prognosis of this condition. We report here a case of IE complicated by kidney injury accompanied by the presence of PR3-ANCA. This young male patient developed fever, acute kidney injury (AKI), haematuria, and proteinuria. Renal biopsy showed crescentic nephritis with tubulointerstitial lesions. However, transthoracic echocardiography and blood culture confirmed IE and ruled out AAV. The patient was managed successfully by surgery and antibiotic treatments. We also discuss the pathological features, therapy, and outcomes based on a literature review of ANCA-positive IE complicated by kidney injury.

Case report

A 22-year-old male patient was admitted to our hospital for fever and elevated serum creatinine (SCr) levels. Two weeks previously, the patient experienced a high fever and visited a local hospital. He was treated with clindamycin and levofloxacin intravenous infusion for 5 days, and his body temperature returned to normal. One week before admission, he experienced a high fever again and went to the local hospital. Routine blood tests showed a white blood cell (WBC) count of 6.15×10^9/L, SCr level of 216 μmol/L, urine protein of 3+, and a urine red blood cell (RBC) count of 145 cells/μL. He had no nasal crusts or arthritis. He was suspected of having acute glomerulonephritis (GN) and was referred to our hospital. There was no abnormal personal or family medical history.

On admission, his body temperature was 37.0°C, respiratory rate was 20 breaths/minute, and blood pressure was 128/51 mmHg. A physical examination did not show any skin rash and superficial lymph nodes were not palpable. The lungs were clear to auscultation bilaterally with no rales, and the heart rate (78 beats/minute) was regular without murmurs, gallops, or rubs. The abdomen was soft without tenderness or rebound pain and the liver and spleen were not palpable. No oedema of the lower limbs was present. Laboratory studies showed the following: proteinuria (2+, 1.8 g/day), a urine RBC count of 116 cells per high-power field (dysmorphic RBCs), no casts in the urine, a blood WBC count of 5.89×10^9/L, a haemoglobin level of 88 g/L, a platelet count of 130×10^9/L, a serum albumin level of 34.1 g/L, a blood urea nitrogen level of 13.55 mmol/L, a SCr level of 160.90 μmol/L, a C-reactive protein

level of 70.15 mg/L, and an erythrocyte sedimentation rate of 59 mm/hour. Laboratory findings for rheumatoid factor, ANCA, anti-hepatitis B antibody, and hepatitis C virus antibody were negative. His antinuclear antibody was 1:100 (cytoplasmic fibre type). His complement C3 (normal range: 0.9–1.8 g/L) and complement C4 (normal range: 0.1–0.4 g/L) levels were 0.25 g/L and <0.067 g/L, respectively. Serum immunoglobulin (Ig) G, IgA, and IgM antibody levels were normal. There were no major abnormalities in the patient's electrocardiogram or lung computed tomography. Urinary system ultrasound showed that the right kidney size was $12.9 \times 4.8 \times 5.5$ cm^3 and the left kidney size was $13.5 \times 7.8 \times 5.6$ cm^3. Digestive system ultrasound identified splenomegaly and no other abnormalities, such as abscesses or an infarction, were found. However, a transthoracic echocardiogram was not performed. The patient did not have fever after admission. A renal biopsy was performed. Fourteen glomeruli were examined by light microscopy and immunofluorescence. Three glomeruli had fibrinoid necrosis and three had segmental cellular crescents. Acute inflammatory tubular lesions and interstitial infiltrate were observed. Deposits of C3 were detected in the glomeruli by immunofluorescence. No electron-dense deposits were observed under the epithelium, in the basement membrane, or under the endothelium by electron microscopy (Figure 1). For suspicion of segmental crescentic GN, 40 mg of methylprednisolone per day was administered intravenously for 7 days, and then the patient was discharged. He took oral prednisone 25 mg/day and oral cyclophosphamide 50 mg twice a day after discharge from the hospital.

During the course of immunosuppressive therapy, the patient's SCr level returned to normal. However, he initially had an elevated body temperature intermittently (37.1°C–37.8°C), and finally experienced a high fever on the 69th day of immunosuppressive therapy. He was admitted to the hospital again. In addition to fever, the patient had manifestations of gross haematuria, fatigue, weight loss, appetite loss, and slight dyspnoea. A physical examination showed a 3/6 grade diastolic murmur at the aortic valve auscultation area. Routine blood tests showed a WBC count of 18.92 $\times 10^9$/L and a normal SCr level (93 μmol/L). The haemoglobin level was 52 g/L, mean RBC volume was 87.4 fL (normal range: 82.0–100.0 fL), mean haemoglobin content was 28.6 pg (normal range: 27.0–34.0 pg), and mean haemoglobin concentration was 327.0 g/L (normal range: 316.0–354.0 g/L). Total bilirubin levels, direct bilirubin levels, urobilinogen levels, a faecal occult blood test, and hepatitis indicators were normal. Bone marrow cytology showed that the neutrophil alkaline phosphatase score was greatly increased. No major abnormalities on a computed tomographic examination of the lungs and abdomen were identified, but transthoracic cardiac ultrasound showed a bicuspid aortic valve, the aortic valve was rough, multiple strong echoes were identified (largest was 15×9 mm), and a large number of reflux signals were detected. The patient's urine RBC count was 1527/μL, and serum complement C3 and C4 levels were <0.18 g/L and <0.068 g/L, respectively. The PR3-ANCA level was 140.1 RU/mL (ELISA, normal range: 0.0–20.0 RU/mL) and the MPO-ANCA level was 6.1 RU/mL (ELISA, normal range: 0.0–20.0 RU/mL). Blood culture was performed three times and all cultures showed *Granulicatella adiacens*. The patient was finally diagnosed with ANCA-positive IE combined with AKI. Prednisone and cyclophosphamide were discontinued, and his SCr level increased to 150 μmol/L again. The patient was then treated with intravenous piperacillin/tazobactam sodium for 4 weeks. Although

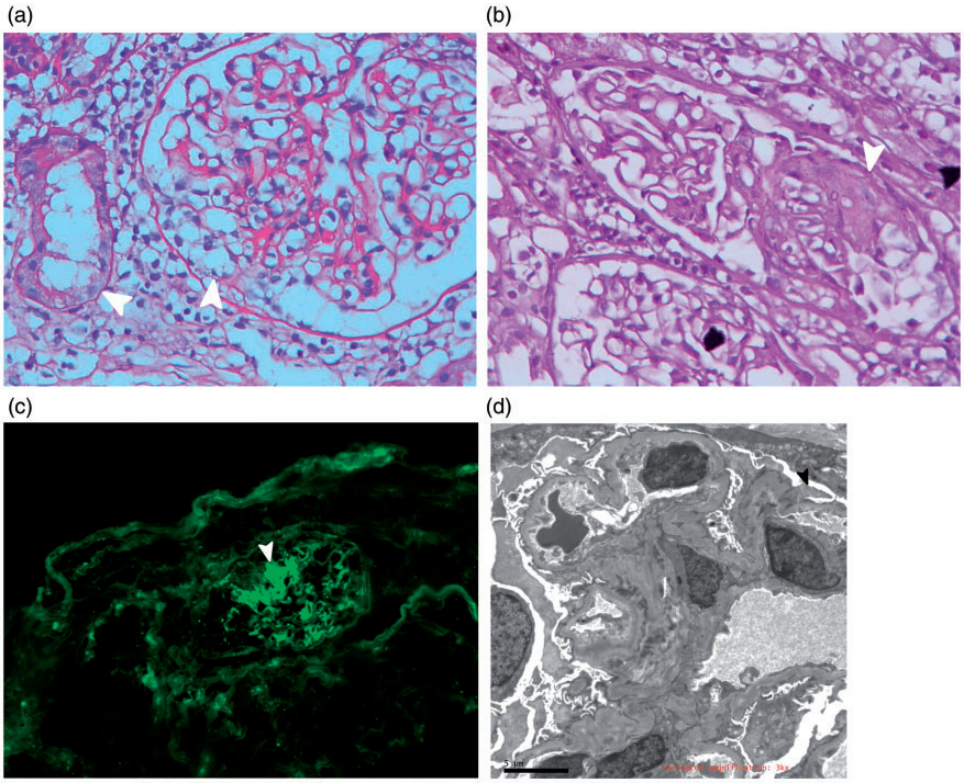

Figure 1. Renal biopsy results of the patient.
Light and electron microscopy of renal biopsy samples. a. Glomerular endocapillary hypercellularity with a segmental cellular crescent can be seen. Renal tubular epithelial cells are flat and the brush border is detached. (haematoxylin and eosin stain, ×400) b. Segmental cellular crescent with fibrinoid necrosis can be seen (arrow), and the mesangial area is not greatly broadened (periodic acid Schiff stain, ×400) c. Mild complement 3 deposits (1+) (arrow) can be seen in the glomeruli (immunofluorescence microscopy, ×200) d. Podocyte processes are partially fused (arrow), and no electron-dense deposits can be seen under the epithelium, in the basement membrane, or under the endothelium (electron microscopy, ×3k).

his fever was controlled, he still had abnormal kidney function and haematuria. The patient then underwent aortic valve replacement and pathology of the excised valve showed white thrombosis with fibrosis and partial calcification. He was subsequently treated with intravenous ceftriaxone for an additional 22 days. Three months postoperatively, SCr, haemoglobin, and PR3-ANCA levels were within the normal range, urine protein was 1+, and the RBC count was 152/μL (Figure 2).

Discussion

The appearance of ANCA in the course of IE complicates diagnosis and treatment, and makes determining the prognosis difficult. Therefore, we conducted a case search and systematic review of this condition. A literature search of previously published cases of ANCA-positive IE with renal biopsy was performed via PubMed and Medline. We used the title and abstract entries "endocarditis" and "ANCA or

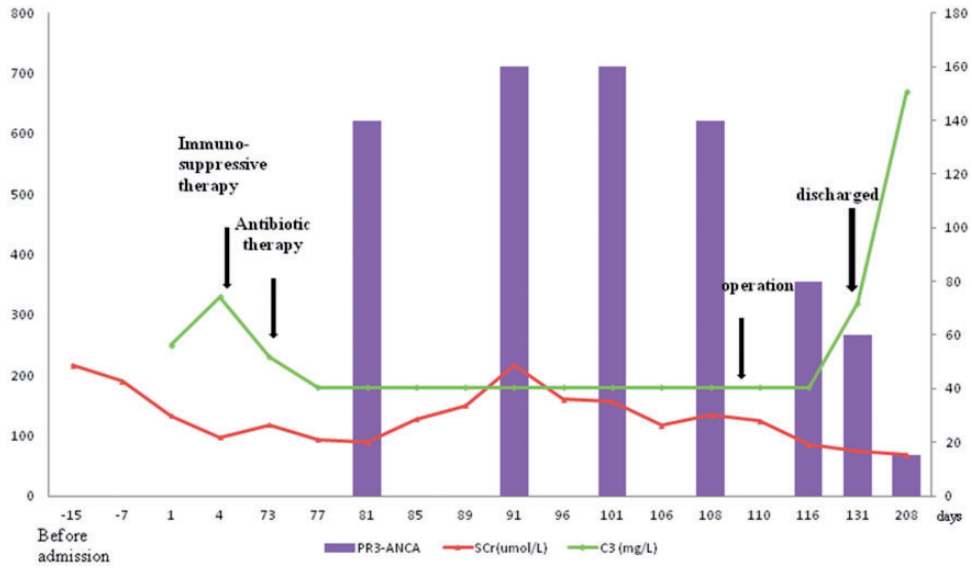

Figure 2. Trend in changes in SCr levels during treatment. SCr levels, C3 levels, and PR3-ANCA titres are shown over the course of the patient's first admission (days). The patient underwent immunosuppressive therapy on the fourth day after admission. The patient's SCr levels recovered and remained normal, but C3 levels continued to decrease. On the 73rd day, the patient's infection worsened. The patient showed persistent PR3-ANCA/c-ANCA positivity, continuous low C3 levels, and gross haematuria. Therefore, after the diagnosis was confirmed on the 73rd day, the immunosuppressant treatment was stopped and antibiotic treatment was initiated, but SCr levels rose again. After 36 days of antibiotic therapy, the patient's temperature fell to the normal range. Surgery was performed on the 109th day of treatment, with subsequent antibiotic therapy for a further 22 days. The ANCA titre gradually decreased, C3 levels increased, while SCr returned to normal levels and gross haematuria disappeared. The PR3-ANCA/c-ANCA titre turned negative on day 208.

Scr, serum creatinine; C3, complement 3; PR3-ANCA/c-ANCA, proteinase-3-antineutrophil cytoplasmic antibody/cytoplasmic staining ANCA.

antineutrophil cytoplasmic antibody" and "renal biopsy," which yielded 26 well documented cases (English language only).[4–28] We added our case to this review and compared clinical features, pathology findings, treatment, and prognosis (Tables 1, 2).

Many pathogens can cause ANCA-positive IE, especially PR3-ANCA-positive IE. According to the literature, the most common pathogen is *Bartonella* (29.6%), followed by *Streptococcus* (22.3%). Our case is currently the only case of ANCA-positive IE caused by *G. adiacens*, which is a nutritionally variant streptococci (NVS) known as a commensal organism in human mouth flora.[29,30] NVS is usually involved in cases of bacterial endocarditis and bacteraemia.[29,30] However, susceptibility testing for NVS is unavailable for most routine clinical laboratories owing to its slow growth and high requirement for nutrient bases. The American Heart Association and British Society for Antimicrobial Chemotherapy suggest that NVS IE should be treated with a combination of benzylpenicillin or ampicillin plus gentamicin for a duration of 4 to 6 weeks.[29,30] Gentamicin was not used in our patient because of impaired renal function. Fortunately, our patient

Table 1. Characteristics of 27 patients (including our case) with ANCA-positive infective endocarditis with kidney injury.

Patients' characteristics	Number (%) (n=27 cases)
Clinical features	
Fever	12 (44.4)
Rash, purpura, and Osler's nodes	6 (22.2)
Non-specific symptoms	24 (88.9)
Arthralgia and myalgia	5 (18.5)
Fatigue	8 (29.6)
Weight loss	6 (22.2)
Appetite loss, nausea, and vomiting	5 (18.5)
Dyspnoea and paroxysmal nocturnal dyspnoea	7 (25.9)
Back pain, oedema, oliguria, nycturia, and gross haematuria	12 (44.4)
Cognitive deterioration	2 (7.4)
Affected organs other than the kidneys and heart	
Lungs	5 (18.5)
Skin	6 (22.2)
Nervous system	4 (14.8)
Spleen	6 (22.2)
Liver	1 (3.7)
Joints	1 (3.7)
Laboratory results	
PR3-ANCA/c-ANCA	24 (88.9)
PR3+MPO	3 (11.1)
Decreased C3 levels	15/15
Pathogen	
Streptococcus	6 (22.2)
MSSA	1 (3.7)
Bartonella	8 (29.6)
MRSA	2 (7.4)
Globicatella sanguinis	1 (3.7)
Aggregatibacter aphrophilus	1 (3.7)
Granulicatella adiacens	1 (our case) (3.7)
Negative blood culture	7 (25.9)
Therapy	
Immunosuppressive therapy	14 (6 patients stopped within 1 month and 8 continued to use*)
Antibiotic therapy	27 (100)
Heart surgery	13 (48.1)
Prognosis	
Recovery	24 (88.9)
Death	3 (11.1)
Negative ANCA	17/17

*One patient misused prednisone and took one tablet a day.

ANCA, antineutrophil cytoplasmic antibody; c-ANCA, cytoplasmic staining ANCA; PR3, proteinase-3; MPO, myeloperoxidase; C3, complement 3; MSSA, methicillin-sensitive *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*.

Table 2. Renal manifestations and morphological characteristics of 27 cases (including our case) of anti-neutrophil cytoplasmic antibody-positive infective endocarditis.

Patients' characteristics	Number (%) (n=27 cases)
Renal manifestation	
Haematuria	1 (3.7)
Aseptic leukocyturia	6 (22.2)
Nephrotic-range proteinuria	3 (11.1)
RPGN	6 (22.2)
Proteinuria and haematuria	25 (92.6)
Proteinuria, haematuria, and RF	22 (81.5)
Renal pathology	
LM	
Crescentic GN	18 (66.7)
Focal segmental GN	11 (40.7)
MPGN	9 (33.3)
Tubular injury and interstitial oedema	11 (40.7)
Mesangial capillary glomerulonephritis	1 (3.7)
Necrosis	3 (11.1)
Pauci-immune GN	6 (22.2)
IF	
IgA	4 (14.8)
IgG	5 (18.5)
IgM	9 (33.3)
C3	14 (51.9)
C1q	6 (22.2)
Negative	10 (37.0)
EM (10 cases)	
Electron-dense deposition	6/10 (60)
Localization of electron-dense deposits	
Mesangial and subendothelial	4
Subendothelial	1
Subepithelial	1
Hump formation	0
No electron-dense deposition	4/10 (40)

RPGN, rapidly progressive glomerulonephritis; RF, renal failure; LM, light microscopy; GN, glomerulus nephritis; MPGN, proliferation of mesangial cells; IF, immunofluorescence; Ig, immunoglobulin; C3, complement 3; EM, electron microscopy.

responded well to semi-synthetic penicillin and ceftriaxone.

A variety of factors can lead to renal impairment in the course of ANCA-positive IE. Molecular mimicry between bacterial and glomerular constituents is likely to be involved.[3] Activation of the plasmin system and direct activation of the alternate complement pathway may produce C3-dominant nephropathy. Another potential mechanism could be the associated ANCA antibody, which is a primary immune complex mechanism in only a minority of patients.[3] With regard to kidney injury, recent studies[31–33] have suggested that ANCA activates indirect pathways involved in C5a receptors by activating neutrophils in microvessels, releasing complement activators, and finally leading to damage to the glomeruli. However, the

specific mechanism of damage produced by ANCA is currently unclear.

With regard to kidney pathology in IE, hypercellularity and proliferation of endothelial and mesangial cells, with immunoglobulin and complement deposition, are present. The most common renal pathology of IE that was identified in our literature review was crescentic GN, which is consistent with previous autopsy reports.[3] This is in contrast to focal, segmental, or diffuse hypertrophic GN, with intracapillary hyperplasia, which was described previously on the basis of data obtained from autopsy reports.[34,35] C3 deposition (51.9%) was prominent in IE with GN, whereas IgG deposition was observed in only 18.5% of cases.[3] Acute tubular injury was also present in many cases (40.7%), and histological red blood cell casts were noted in more than half of the cases. However, no cases of eosinophilic allergic interstitial nephritis were observed.[3] As with AAV, focal and segmental necrotizing crescentic GN, which classically is pauci-immune, is also present in IE. In ANCA-positive IE, we found that electron microscopy showed electron-dense deposits in the subendothelial or mesangial areas. There were few subepithelial deposits and hump-like electron-dense deposits, and deposits were not found in 40% cases. At this time, identifying whether ANCA is involved in pathological kidney damage is difficult. However, kidney biopsy is important in the differential diagnosis of IE and AAV.

In addition to kidney pathology, there are some subtle clues that are useful for differential diagnosis between ANCA-IE and AAV. Patients with ANCA-positive IE with kidney injury are mostly elderly (>50 years), and the aortic valve and mitral valve are commonly affected, as found in our patient.[4,36] The presence of multiple valve involvement may be a predictive marker of IE rather than AAV in ANCA-positive patients. Endocarditis as a manifestation of AAV is rare.[20] Fever (≥38°C) and weight loss are more frequent in patients with ANCA-positive IE than in those with AAV.[36] Pulmonary and articular signs are less common in patients with ANCA-positive IE than in those with AAV. Splenic infarction, which is rare in AAV, occurs in 25% of patients with ANCA-positive IE,[37–39] while thrombocytopenia[14] and cerebral embolism are highly indicative of ANCA-positive IE rather than AAV.[20,28,40] PR3-ANCA positivity and hypocomplementemia are more common in ANCA-positive IE than in AAV.[3,14,36]

Eight patients from our literature review received immunosuppressive therapy and achieved excellent results.[9,11,15,17,22–25] Successful treatment mainly manifests as recovery of renal function and even removal of haemodialysis treatment. However immunosuppressive treatment needs to be carried out under strong and effective antibiotic treatments; otherwise, immunosuppression may aggravate systemic infection.[41,42] Some studies have reported that the potentially adverse renal outcome of crescentic GN or severe diffuse proliferative GN is a strong indication for administering immunosuppressive therapy and it is associated with renal recovery without worsening IE when combined with antibiotics.[41,43,44] Most effectively treated patients with ANCA-positive IE had favourable outcomes. Previous reports indicated that IE was cured and ANCA became negative within 1 to 8 months.[45] Additionally, renal function greatly improved or returned to normal levels 6 weeks to 4 months after treatment. Some patients only showed microscopic haematuria and/or mild proteinuria during the 4 to 6 years of follow-up. In contrast, AAV has frequently been reported to involve focal necrotizing GN and results in significant morbidity and mortality.[45]

Our patient had no symptoms or signs of heart failure during the first hospitalization, and he did not undergo a cardiac ultrasound examination. This resulted in confusion regarding the diagnosis of IE for the second admission to hospital. However, after radical treatment of IE, the patient's renal function recovered, haematuria disappeared, and anaemia and hypocomplementemia were also corrected. Therefore, we believe that our patient had IE at the first admission.

In conclusion, patients with repeated fever, weight loss, continued worsening anaemia, and hypocomplementemia should be suspected of having IE, but AAV also needs to be excluded, particularly in the presence of ANCA. ANCA may be involved in pathological renal damage. With ANCA-positive IE, although immunosuppressive therapy is controversial, immunosuppressive therapy in combination with antibiotic treatment may be beneficial for recovery of renal function. However, these conclusions need more clinical cases to be verified in the future.

Ethics statement

This case report was approved by the Ethics Committee of The Affiliated Hospital of Qingdao University (QYFYWZLL25642) and was in accordance with the principles of the Declaration of Helsinki. Verbal and written informed consent were obtained from the patient for publication of the patient's information before submission.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

ORCID iD

Wei Zhang https://orcid.org/0000-0001-7233-6062

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