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CASE REPORT

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Pauci-immune necrotizing glomerulonephritis in a 24-year-old female with negative ANCA antibodies: A rare case report

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Key Clinical Message

Pauci-immune necrotizing glomerulonephritis (PING) is a small vessel renal vasculitis usually associated with the presence of antineutrophil cytoplasmic antibodies (ANCA) against myeloperoxidase or proteinase. A small proportion of PING patients do not have ANCA antibodies.

Abstract

A condition known as Pauci-immune necrotizing glomerulonephritis, or PING for short, is a type of kidney inflammation that affects small blood vessels. This condition is typically linked with the existence of certain antibodies, specifically antineutrophil cytoplasmic antibodies or ANCA, which target myeloperoxidase or proteinase. However, it's worth noting that a minor percentage of individuals diagnosed with PING do not possess these ANCA antibodies. A 24-year-old woman with no previous medical history arrived at the ER due to various symptoms including joint pain, fever, difficulty swallowing, and shortness of breath. Despite multiple symptoms suggesting systemic lupus erythematosus (SLE), this diagnosis was ruled out based on the EULAR/ACR 2019 classification criteria and laboratory tests. Other potential diagnoses such as rheumatoid arthritis (RA) and eosinophilic garnulomatosis with polyaniitis (EGPA) were also excluded based on respective criteria. The patient was treated with a 3-day course of methylprednisolone, followed by prednisolone, which improved her creatinine levels. Subsequent tests for P-ANCA and C-ANCA were negative. A kidney biopsy confirmed necrotizing glomerulonephritis, consistent with pauci-immune vasculitis. A bronchoscopy revealed bleeding and hemorrhage in her lungs, but bacterial culture analysis was negative. The patient was given piperacillin, tazobactam, and vancomycin for septic coverage, as well as intravenous immunoglobulin (IVIg), which led to symptom improvement.

KEYWORDS
antineutrophil cytoplasmic antibodies (ANCA), computed tomography (CT), pauci-immune necrotizing glomerulonephritis (PING), vasculitis

1 | INTRODUCTION

Antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV) is a rare systemic disorder with different phenotypes that can occur at any age and affect 20–25 people per million per year in Europe.[1]

AAV diseases include microscopic polyangiitis, granulomatous polyangiitis (GPA, formerly "Wegener's granulomatosis"), and eosinophilic granulomatous polyangiitis (EGPA, formerly "Churg-Strauss syndrome").[2]

However, up to 10% of patients with small vessel vasculitis have a clinically negative ANCA test. In contrast, false positive results can occur in the general population and in the setting of infections, malignancies, and autoimmune gastrointestinal and renal diseases.[3]

"Pauci-immune crescentic necrotizing GN" is defined histologically by glomerular fibrinoid necrosis or crescent without significant glomerular immune deposit (immunoglobulin or C3). This type of GN, which represents a frequent cause of acute renal failure, is due to small vessel vasculitis. It occurs during systemic diseases such as microscopic polyangiitis (MPA), Wegener's granulo matosis (WG) and more rarely Churg-Strauss syndrome or as a renal-limited vasculitis (RLV).[4]

Indirect immunofluorescence (IIF) [p-ANCA for myeloperoxidase (MPO); c-ANCA for proteinase 3 (PR3)] is highly sensitive to identify ANCA, in active untreated WG or MPA, with a positive test in >75%–90% of patients.[5] A pathogenic role of ANCA in vasculitis is suspected upon: murine model, vertical transmission of ANCA MPO from pregnant woman to her child and the correlation between ANCA and disease activity.[6] However, in a significant number of cases of pauci immune crescentic GN, ANCAs are absent. Earlier studies, comparing those with ANCA-positive cases suffer, because ANCA-negative groups are small or heterogeneously defined.[5]

2 | CASE PRESENTATION

2.1 | Case history

A 24-year-old female with no past history presented to the emergency department for arthralgia, fever, dysphagia, and dyspnea 4 days ago. The symptoms began as arthralgia in the knees and ankles for 5 months. The pain gets worse during periods of rest and improves with movement, accompanied by swelling and morning stiffness lasting for approximately 30 min. The patient also reported a history of recurrent oral thrush occurring approximately three times a month. 1 month after the onset of symptoms, the patient asked for medical consultation, leading to laboratory tests. She was treated with oral iron therapy for iron-deficiency anemia with Prednisolone 40 mg for 1 month, which partially improved her symptoms. Gradually, the patient tapered off the steroids, stopping them several days prior to admission. The medical history of the patient included only one cesarean section and 40 mg of Prednisolone. The vital signs were normal.

The clinical examination revealed pallor, pharyngitis, and a fine crackle at the base of the right lung. There was synovial thickening in the knees, ankles, proximal interphalanges of the left second and fourth toes, and the right third toe's proximal intraphalanges joint. Pain was noted with all wrist movements, the knees, and the ankles.

2.2 | Differential diagnosis, investigations, and treatment

The examination of the cardiovascular system and the echocardiogram (ECG) were normal without any signs of deep vein thrombosis (DVT). Also, the examination of the neurological and gastrointestinal systems, as well as the skin and lymph nodes, was normal. The results of the laboratory analysis showed that the white blood cell count (WBC) was 15,200/mm^3, while the neutrophils were at 64%, lymphocytes at 22%, eosinophils at 22%, and monocytes at 2%. The neutrophil-to-lymphocyte ratio (N/L) was determined to be 81/9. The red blood cell count (RBC) was 2.6×10^6/mm^3. The hemoglobin (Hb) level was 6.6 g/dL, while the hematocrit (Ht) was 20.3%. The mean corpuscular volume (MCV) was 77.5 fL, and the mean corpuscular hemoglobin (MCH) was 25.5 pg. The results also showed that the iron (Fe) level was 12 mcg/dL, the serum creatinine level was 1.8 mg/dL, and the C-reactive protein (CRP) level was 8.3 mg/L. The levels of Fe were 12 mcg/dL, serum creatinine was 1. 8 mg/dL, CRP was 8.3 mg/L, and the erythrocyte sedimentation rate (ESR) was increased to 75 mm/h. The urine and sediment analysis showed microscopic hematuria(800 red blood cell counts), proteinuria, 70 white blood cells, and bacteria were positive. During the first week of hospitalization, creatinine and Hb levels remained consistent with the values presented above.

Coronal computer tomography (CT) images show multifocal patchy centrilobular consolidative opacities in the bilateral middle lobes and lower lobes, accompanied by acute hemorrhage or infection because of lung vasculitis (Figure 1). The bronchoscopy examination was normal. A bronchial lavage was obtained, and the results of mycobacterial culture and gene expert testing were negative. The presence of Koch's bacillus in the sputum was examined for three consecutive days, and the result was negative. A tuberculin skin test was also negative. In order to investigate the possibility of bleeding, the patient refused to have upper and lower gastrointestinal endoscopies. Additionally, a diffusing capacity of the lung for carbon monoxide (Dlco) test was not conducted because it was not available.

The patient was initiated on a therapeutic regimen consisting of piperacillin, tazobactam, and levofloxacin medications. Staphylococcus aureus was identified through the examination of the sputum culture. The blood culture was negative. The urine culture demonstrated the presence of *Escherichia coli*, which exhibited sensitivity to specific antibiotics such as amikacin, imipenem, and meropenem. Cilastatin and imipenem were used in place of piperacillin and tazobactam, while levofloxacin therapy was continued after consulting with the infectious disease specialists.

Renal ultrasonography was normal. A 24-h urine collection is recommended in addition to rehydration based on urinary output, with an additional intake of 500 mL. It is advised to monitor for sepsis and perform a re-evaluation of urine and sediment. Furthermore, the purpura on the lower extremities appeared, particularly the feet. The CXR revealed the persistence of the same existing infiltrates without any improvement (Figure 2).

Despite several clinical manifestations suggestive of systemic lupus erythematosus (SLE), the possibility of this diagnosis was excluded based on the EULAR/ACR 2019 classification criteria. Also, the laboratory tests revealed that the antinuclear antibody (ANA) levels of 1/40 and negative double-stranded DNA (dsDNA) antibody tests, as well as complement component levels of C3 are 155 (within the normal range of 90–180) and C4 are 31.1 (within the normal range of 10–40), supporting this conclusion. The tests of the antibodies against citrullinated proteins (ACPAs) and rheumatoid factor (RF) were negative, which excluded the diagnosis of rheumatoid arthritis (RA) based on the 2010 ACR/EULAR criteria for early RA. also The EGPA was excluded according to the classification criteria for eosinophilic garnulomatosis with polyaniitis for the 2022 American College of Rheumatology/European Alliance of Rheumatology. Our patient has hematuria and a blood eosinophil count $\geq 1 \times 10^9$/L, which gives her a score of 4, and the score that we needed for confirmation of the EGPA is ≥6.

The patient received a 3-day course of 1 g of methylprednisolone. After that, she receives 1 mg/kg of Prednisolone, which improves the patient's creatinine levels. Furthermore, relevant tests were conducted, revealing negative results for P-ANCA (2.6) and C-ANCA (2.1), which were still negative after retesting them again. Subsequently, a kidney biopsy was conducted on the patient. and received are fragments of tan white tissue submitted in part for IF and the remaining for light microscopy and special stains. MICROSCOPIC DESCRIPTION: The biopsy material comprises fragments of renal cortex containing 14 glomerules, one of which is totally hyalinized. The remaining glomeruli show cellular crescents in two glomeruli and necrosis in four glomeruli. One glomerulus shows segmental scars, and one shows cellular crescents. The interstitium shows inflammatory infiltrates. The trichrome stain shows edema with interstitial fibrosis in 15%. The tubules show acute tubular injury. The blood vessels show marked fibrinous necrosis. The Congo red stain is negative for amyloid. Immunofluorescence: Four glomeruli showing no evidence of immunoglobulins or complement components. The diagnosis was necrotizing glomerulonephritis (GN), consistent with pauci-immune vasculitis (Figure 3). A bronchoscopy was performed, revealing bleeding in the right middle lobe and hemorrhage in the left lower lobe, while the remaining regions appeared normal. Subsequently, a bronchial lavager was collected for bacterial culture analysis. The patient was initiated on septic coverage with piperacillin, tazobactam, and vancomycin. Additionally, intravenous immunoglobulin (IVIg) at a dosage of 400 mg/kg was commenced within 5 days, resulting in clinical symptom improvement.

2.3 | Outcome and follow-up

The patient was transferred to the articular division for comprehensive coverage. The bacterial culture analysis of the bronchial lavager and the urine were negative. The septic coverage was discontinued, and the patient's treatment regimen was switched to mycophenolate mofetil (MMF) at a dosage of 2 g per day with a gradual reduction in the dosage of Prednisolone. At the time of discharge, vital signs and laboratory tests were normal.

3 | DISCUSSION

The ANCA associated vasculitides (AAV) are a collection of relatively rare autoimmune diseases of unknown cause, characterized by inflammatory cell infiltration causing necrosis of blood vessels. The AAV comprise granulomatosis with polyangiitis (GPA, previously known as Wegener's

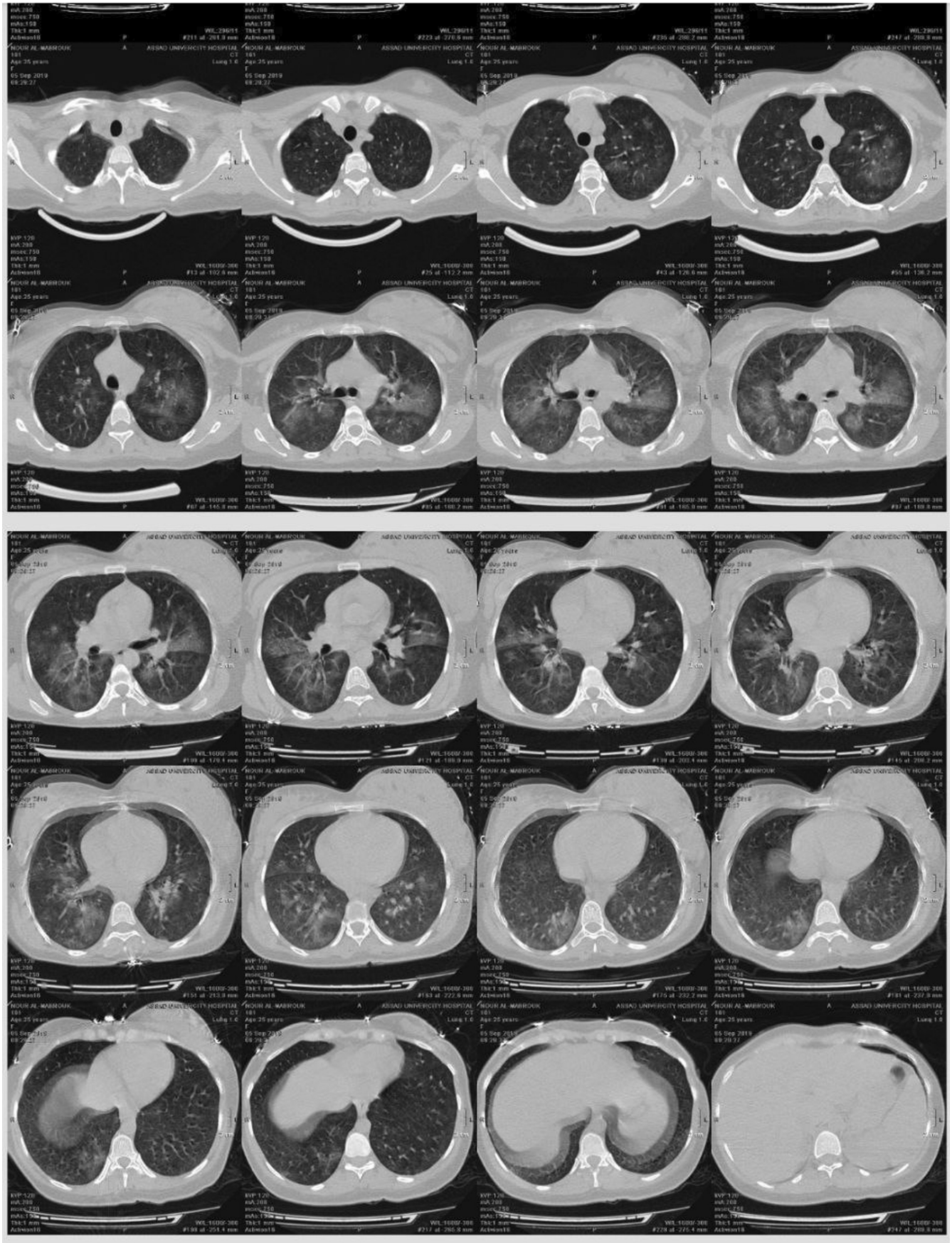

FIGURE 1 Coronal CT images show multifocal patchy centrilobular consolidative opacities in bilateral middle lobes and lower lobes, consistent with acute hemorrhage or infection.

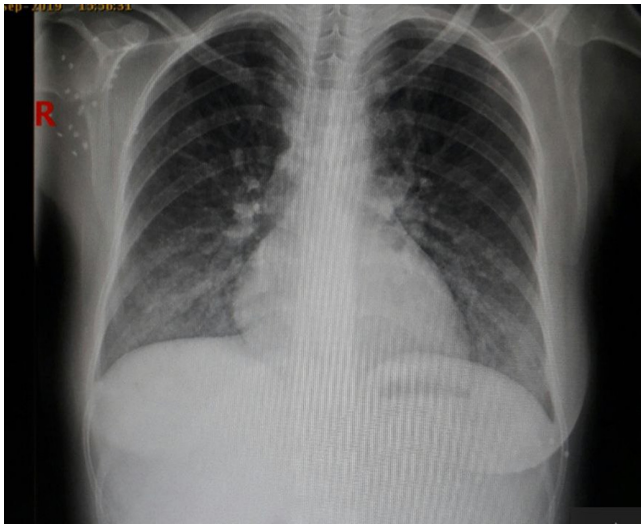

FIGURE 2 The CXR reveals the persistence of the same existing infiltrates without any improvement.

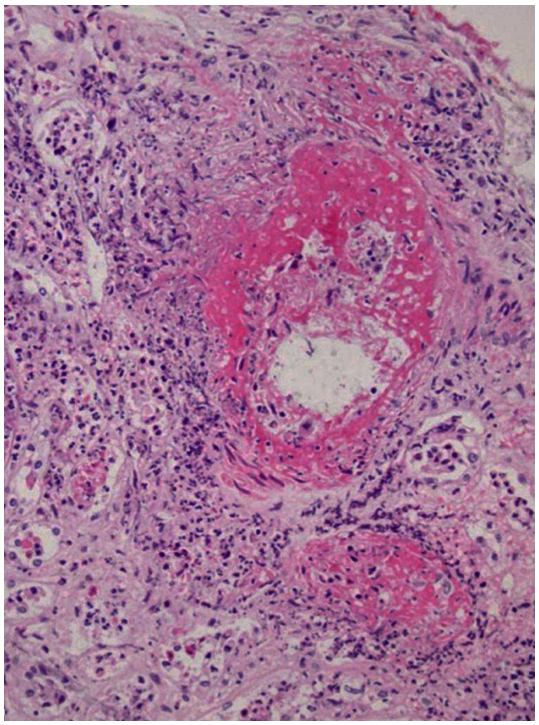

FIGURE 3 Renal biopsy showing diffuse tubulointerstitial inflammation and extensive necrosis destroying the normal structure of the tubules and glomeruli by light microscopy (hematoxylin–eosin stain, original magnification 200×).

granulomatosis), MPA and eosinophilic granulomatosis with polyangiitis (EGPA, previously known as Churg-Strauss syndrome).[6,7]

Pauci-immune crescentic necrotizing GN is defined histologically by the presence of focal glomerular necrosis and extra capillary proliferation in the absence of significant glomerular immune deposits. This type of GN, which represents a frequent cause of acute renal failure, is due to small vessel vasculitis.[8]

Pauci-immune necrotizing small vessel vasculitis is usually associated with the presence of ANCAs directed to proteinase 3 (PR3-ANCA) or myeloperoxi-dase (MPO-ANCA). More rarely ANCA's are absent in this type of vasculitis.

ANCA-negative cases are more commonly found among those with limited disease, that is, disease confined to the upper and lower respiratory tracts and not affecting the kidneys,[9] unlike presented the case.

The clinical spectrum of the AAV is broad and hence the presentation can be quite varied,[7] such as weight loss, malaise, fatigue, arthralgia, and myalgia relating to the systemic autoimmune pathophysiology. Although any tissue can be involved in AAV, the upper and lower respiratory tract and kidneys are most commonly and severely affected, followed by skin, gastrointestinal, cardiac, and nervous systems.[10,11]

The clue to the diagnosis is often developing multisystem involvement; therefore, a very careful and systematic approach is required to make the diagnosis. A detailed history and examination is required; laboratory investigations should include assessments of inflammatory markers, kidney function (urea and electrolytes—always with urine dip assessment, quantification of urine protein leak, and urine microscopy for red cell casts), serological testing including ANCA, antinuclear antibodies, and anti-glomerular basement membrane antibodies (both SLE and Goodpasture's syndrome can masquerade as AAV). Infection should also be excluded and the diagnosis of bacterial endocarditis considered and excluded. Chest X-ray should be undertaken. Computerized tomography or magnetic resonance imaging may be required to assess the chest, brain, orbits and ear, nose and throat structures in more detail. A biopsy should always be considered to confirm the diagnosis and exclude mimics. However, treatment should not necessarily be delayed simply to get a biopsy.[7]

Our patient's urine analysis revealed 70 white blood cells, 800 red blood cell counts, and protein.

CT images show multifocal patchy centrilobular consolidative opacities in the bilateral middle lobes and lower lobes, consistent with acute hemorrhage or infection.

Pulmonary renal syndrome was suspected and P-ANCA C-ANCA was negative. The kidney biopsy was consistent with the Pauci-immune crescentic GN type that is usually found with AAV.

The average expected length of survival in GPA without treatment is 5 months.[9]

The goal of induction therapy is to achieve remission by 3 months that is sustained. Treatment should be

initiated as soon as a diagnosis of AAV is at least probable and appropriate safety investigations have been performed. Initiation of treatment, especially in the setting of severe renal or lung disease, should not be delayed obtaining a biopsy, as several days of treatment usually does not markedly reduce the diagnostic yield of a biopsy. The combination of glucocorticoids with either cyclophosphamide or rituximab is the current standard of care for induction of remission for severe disease.[11]

After successful remission induction, guidelines recommend withdrawing the initial immunosuppressive agent and commencing a maintenance regimen with azathioprine or methotrexate.[7] The goals of maintenance therapy are to prevent relapse. Many patients with AAV require prolonged low-dose glucocorticoids (prednisone ≤10 mg daily) to maintain remission, even if also treated with rituximab.[11]

Early cessation of therapy (<1 year) is associated with an increased risk of relapse. It is generally advised that maintenance therapy is continued for at least 18–24 months before being gradually withdrawn. Attempts at reduction of glucocorticoids should be made prior to tapering of the immunosuppressive remission maintenance agent.[7]

The reported patient was given a three-day course of 1 g of methylprednisolone and then received 1 mg/kg of prednisolone, which progressively improved his creatinine levels. Soon after, the patient began using MMF at a dose of 2 g daily while gradually lowering the prednisolone dosage.

Age has important bearing on the prognosis of ANCA negative systemic vasculitis. In Ute Eisenberger's series age above 65 years was associated with high mortality. The age in our patient is considerably younger and she has fared better due to the fact that MMF was used more often. MMF is increasingly being found useful in the induction and remission phases of systemic vasculitides.[9]

After successful remission induction, guidelines recommend withdrawing the initial immunosuppressive agent and commencing a maintenance regimen with either azathioprine or methotrexate.[7] The goals of maintenance therapy are to prevent relapse, to minimize the risk of comorbidities and drug toxicity, and to manage the consequences of organ damage, such as chronic kidney disease. Many patients with AAV require prolonged low-dose glucocorticoids (prednisone ≤10 mg daily) to maintain remission, even if also treated with rituximab or an oral/span> immunosuppressive drug.[11]

Early cessation of therapy (<1 year) is associated with an increased risk of relapse. It is generally advised that maintenance therapy is continued for at least 18–24 months before being gradually withdrawn. In general, attempts at reduction of glucocorticoids should be made prior to tapering of the immunosuppressive remission maintenance agent.[7,12,13]

Our patient was given a 3-day course of 1 g of methylprednisolone and then received 1 mg/kg of prednisolone, which progressively improved his creatinine levels. Soon after, the patient began using MMF at a dose of 2 g daily while gradually lowering the prednisolone dosage.

4 | CONCLUSION

PING with negative ANCA antibodies is a type of kidney disease characterized by inflammation and damage to the glomeruli (the filtering units of the kidneys) with minimal immune deposits. This condition is typically associated with a lack of ANCA, which are commonly found in other types of necrotizing GN.

The absence of ANCA antibodies in this condition can make it challenging to diagnose, as ANCA-negative PING may not present with the typical signs and symptoms seen in AAV. Treatment for this condition usually involves immunosuppressive medications to reduce inflammation and preserve kidney function. It is important for individuals with this condition to be closely monitored by a nephrologist to manage their kidney health and prevent further damage.

AUTHOR CONTRIBUTIONS

Suaad Hamsho: Writing – review and editing. **Sumaya Dumirieh:** Writing – review and editing. **Mouhammed Sleiay:** Writing – original draft; writing – review and editing. **Douha AlBaroudi:** Writing – original draft; writing – review and editing. **Muhamad Ali Alshekh:** Writing – original draft. **Marwa Alahmad:** Writing – review and editing.

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DATA AVAILABILITY STATEMENT

Not applicable.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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