














CASUISTIC PAPER

## Unmasking the nature of granulomatosis with polyangiitis – a diagnostic odyssey revealed through a compelling case report

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### ABSTRACT

**Introduction and aim.** Granulomatosis with polyangiitis (GPA), formerly known as Wegener's granulomatosis, presents a formidable challenge in the realm of autoimmune diseases.

Granulomatosis, characterized by vasculitis and granuloma formation, exhibits diverse clinical manifestations. The rarity of GPA is evident, with an estimated incidence between 0.4 and 11.9 cases per 1 million person-years. The aim of this report is to show the complex diagnostic challenges inherent in GPA, demonstrating the diagnostic process from initial symptoms.

**Description of the case.** This case report unfolds the diagnostic journey of a 52-year-old Caucasian male. The presented case, initially suspected as a respiratory infection, led to a comprehensive investigation owing to persistent symptoms, abnormal blood counts, and elevated inflammatory markers. This narrative aims to depict the patient's diagnostic journey. Key diagnostic tools include ANCA testing, imaging studies, and tissue biopsy. Pulmonary nodules, lymphangitic changes, and renal involvement culminating in a GPA diagnosis confirmed by positive ANCA and anti-PR3 antibodies. The successful management of this case involved a tailored therapeutic regimen, including cyclophosphamide and methylprednisolone, addressing both vasculitic and renal components.

**Conclusion.** This case contributes to the understanding of atypical presentations of GPA, emphasizing the importance of a holistic and dynamic diagnostic approach.

**Keywords.** autoimmune diseases, granulomatosis with polyangiitis, vasculitis

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## Introduction

Granulomatosis with polyangiitis (GPA), previously known as Wegener's granulomatosis, stands as a challenging autoimmune disease.<sup>1</sup> It is characterized by the inflammation of small- to medium-sized blood vessels (vasculitis) and the formation of granulomas in various organs.<sup>2</sup> In this case, we would like to present the journey of a patient's diagnostic path, which serves as a striking example of the difficulties in identifying this disorder.

Granulomatosis is a rare autoimmune disease with a relatively low incidence, estimated to range between 0.4 and 11.9 cases per 1 million people per year.<sup>3</sup> It affects individuals across both genders, with equal numbers of males and females.<sup>3</sup> Onset of this disease typically occurs between the ages of 45 and 65 years.<sup>3</sup> There is a higher prevalence of GPA among individuals of White ethnicity.<sup>3</sup> Notably, the incidence of GPA appears to have increased in recent decades, possibly due to greater awareness and improved diagnostic capabilities, particularly with the introduction of ANCA (anti-neutrophil cytoplasmic antibody) testing.<sup>4</sup> In a Polish study, 1491 patients (749 females and 742 males), all of whom were admitted to the hospital for the first time with a diagnosis of GPA, was conducted between 2011 and 2015. The average annual incidence of GPA in Poland was estimated at 7.7 cases per million within the population (95% CI, 4.1–11.4), and the point prevalence stood at 38.4 cases per million at the end of 2015.<sup>5</sup> Interestingly, it was observed that the highest rate of newly diagnosed GPA cases occurred during the month of January.<sup>5</sup> This temporal pattern in GPA incidence warrants further investigation to better understand the potential seasonal variations and contributing factors to the disease's occurrence.<sup>6</sup>

Antineutrophil cytoplasmic antibodies (ANCA) play a crucial role in the pathogenesis and diagnosis of GPA.<sup>7</sup> ANCA antibodies are a hallmark feature of GPA and are central point to understanding the autoimmune nature of this condition.<sup>8</sup> In GPA, the immune system mistakenly produces ANCA antibodies, specifically proteinase 3 (PR3-ANCA).<sup>8</sup> When ANCA antibodies bind to neutrophils, they activate these immune cells, leading to the release of inflammatory mediators and the initiation of an autoimmune response.<sup>9</sup> The activated neutrophils adhere to the blood vessel walls, contributing to inflammation and damage to the small- to medium-sized blood vessels in various organs.<sup>9</sup> PR3-ANCA is particularly indicative of GPA.<sup>10</sup> ANCA testing is often used to support the clinical diagnosis of GPA, especially when other clinical and laboratory findings are suggestive of the disease.<sup>11</sup>

The symptoms of GPA can vary widely from one individual to another and may affect multiple organ systems.<sup>12</sup> Common symptoms of GPA include constitutional signs such as fever, asthenia, recurrent low-grade

fevers, and weight loss, with approximately 50% of patients experiencing these manifestations, which contributes to the complexity of its clinical presentation.<sup>2</sup>

Ear, nose and throat (ENT) signs are present in 70%, even up to 100% of cases at diagnosis.<sup>2</sup> Respiratory symptoms are prevalent, including chronic sinusitis, rhinitis, and a persistent cough with blood-tinged sputum. Shortness of breath may arise due to lung involvement, which affects 50% to 90%.<sup>2</sup> Renal symptoms, occurring in a significant percentage of cases, manifests with hematuria and proteinuria, often presenting as focal segmental necrotizing glomerulonephritis accompanied by extracapillary proliferation and pauci-immune crescent formation.<sup>13</sup>

Musculoskeletal symptoms could be present in two-thirds of patients at the onset of the disease involve joint pain and swelling.<sup>14</sup> Cutaneous manifestations are reported in approximately 23% of patients, including skin rashes, ulcers, and purpura resulting from blood vessel inflammation.<sup>2,15</sup> Ocular symptoms encompass eye inflammation, with potential complications such as redness, pain, and vision changes.<sup>16</sup> Neurological involvement, though less frequent, may lead to headaches, peripheral neuropathy, and severe neurological complications.<sup>17</sup>

To classify a patient with a diagnosis of small- or medium-vessel vasculitis as having GPA, the cumulative score had to be equal to or exceed 5 points. These criteria provide a valuable tool for accurately diagnosing GPA while distinguishing it from other vasculitis and vasculitis mimics (Table 1).<sup>18</sup>

**Table 1.** The classification criteria for GPA<sup>18</sup>

Criteria	Points
Bloody nasal discharge, nasal crusting, or sino-nasal congestion	3
Cartilaginous involvement	2
Conductive or sensorineural hearing loss	1
Cytoplasmic antineutrophil cytoplasmic antibody (ANCA) or anti-proteinase 3 ANCA positivity	5
Pulmonary nodules, mass, or cavitation on chest imaging	2
Granuloma or giant cells on biopsy	2
Inflammation or consolidation of the nasal/paranasal sinuses on imaging	1
Pauci-immune glomerulonephritis	1
Perinuclear ANCA or antimyeloperoxidase ANCA positivity	-1
Eosinophil count $\geq 1 \times 10^9/L$	-4

Researchers are exploring various strategies for the treatment of autoimmune diseases such as GPA and eosinophilic GPA (EGPA).<sup>19</sup> These investigations encompass evaluating the advantages of higher-dose glucocorticoid (GC) therapy over standard dosing in terms of faster inflammation control and potential reductions in relapses.<sup>19</sup> Prolonged use of GCs increases the risk of various adverse effects.<sup>20</sup> Recent trials assessing induction

therapy in GPA have encompassed both new-onset and relapsing patients.<sup>21</sup> Notably, in the largest trial comparing rituximab (RTX) and cyclophosphamide (CYC) for remission induction, relapsing patients exhibited higher remission rates at 6 and 12 months with RTX.<sup>21</sup> In contrast, patients in the CYC arm were switched to receive azathioprine (AZA) for 12–15 months.<sup>22,23</sup> Consequently, RTX is favored for treating relapsing patients.<sup>21</sup>

Researching novel immunomodulators like JAK inhibitors as alternative therapies, potentially offering fewer side effects but requiring a thorough evaluation for safety and potential unknown risks.<sup>24</sup> Gaining insights into the long-term effectiveness and safety of avacopan as an induction and maintenance therapy compared to standard treatments, understanding potential limitations or side effects.<sup>25</sup> C5a blockade can replace GCs for induction and extended use, reducing the adverse effects associated with long-term GC therapy while considering potential limitations.<sup>25</sup> These research objectives aim to enhance the treatment of autoimmune diseases, striving to optimize therapeutic benefits while minimizing potential harm and side effects.<sup>19</sup>

## Aim

The aim of this report is to offer a comprehensive view of the diagnostic journey for GPA, emphasizing the efficiency of the diagnostic process. The selected case serves as an illustration of the typical diagnostic challenges associated with GPA, detailing the progression from the onset of symptoms to the eventual identification of the disease. By presenting this case, we hope to shed light on the various pitfalls, missteps, and frustrations that often accompany the diagnosis of GPA, ultimately serving as a valuable resource for medical practitioners.

## Description of the case

The patient, a 52-year-old male, presented for the first time to his family doctor in early April with a persistent dry cough and weakness lasting for two weeks that was diagnosed as an upper respiratory tract infection. He had no history of chronic illnesses, but experienced occasional generalized joint pains, self-treated with NSAIDs. In his medical history, there was a 20-cigarette-per-day smoking habit and excessive alcohol consumption (1–2 beers per day). The doctor prescribed a syrup with levodropropizine and doxycycline. The patient was referred for tests (complete blood count, CRP, creatinine, lipid profile, and glucose concentration) with a follow-up appointment scheduled in 3 days).

The test results revealed leukocytosis  $12.3 \times 10^3/\mu\text{L}$  (normal range:  $4.2\text{--}9.1 \times 10^3/\mu\text{L}$ ), significant thrombocytosis  $527 \times 10^3/\mu\text{L}$  (normal range:  $<450 \times 10^3/\mu\text{L}$ ), elevated CRP 5.42 mg/dL (normal range: 0–5 mg/dL) and increased glucose levels 6.08 mmol/L (normal range: 3.9–5.5 mmol/L). Other results, including creatinine,

were within normal ranges. In mid-May, the patient returned with generalized musculoskeletal pain, tenderness, restricted mobility in shoulder and elbow joints, and bilateral hand numbness. Symptomatic treatment was initiated: etoricoxib 60 mg tablets, diclofenac in a series of 10 injections (75 mg/3 mL), and a supplement containing vitamins B12, B6, thiamine. A follow-up consultation was scheduled for a week later. During the follow-up, the patient still experienced pain and numbness, fever (up to 39°C), and loss of appetite. He reported a weight loss of approximately 10 kg in 2 months. Urgent referral to the internal medicine department was made for further diagnostic investigation.

Upon admission, the patient was generally in good condition, tachycardic (110/min), without peripheral edema but with slightly enlarged supraclavicular and axillary lymph nodes on the left side and erythematous lesions with desquamation on the upper back. Laboratory tests showed leukocytosis  $15.25 \times 10^9/\text{L}$  (normal range:  $4.9\text{--}9.1 \times 10^3/\mu\text{L}$ ), mild normocytic anemia 10.6 g/dl (normal range: 13.7–16.5 g/dL), significant thrombocytosis  $1069 \times 10^9/\text{L}$  (normal range:  $<450 \times 10^3/\mu\text{L}$ ), elevated ESR 69 mm/h (normal range: 1–20 mm/h), CRP 213.3 mg/L (normal range: 0–5 mg/dL), hyperuricemia 566  $\mu\text{mol}/\text{L}$  (normal range: 202–417  $\mu\text{mol}/\text{L}$ ), hyperkalemia 6.3 mmol/L (normal range: 3.5–5.1 mmol/L), D-dimer 6.99  $\mu\text{g}/\text{mL}$  (normal range: 0–0.5  $\mu\text{g}/\text{mL}$ ), and positive rheumatoid factor (RF) at 184.4 IU/mL (normal range:  $<14$  IU/mL). Protein and albumin levels in serum were decreased. Kidney parameters revealed an elevated creatinine concentration of 387.7  $\mu\text{mol}/\text{L}$  (normal range: 62–106  $\mu\text{mol}/\text{L}$ ), with an eGFR of 15.14 mL/min/1.73 m<sup>2</sup> (normal range:  $>90$  mL/min/1.73 m<sup>2</sup>), and urea of 16.9 mmol/L (normal range: 2.76–8.07 mmol/L). The urinalysis revealed the absence of bacteria, leukocyturia, and significant proteinuria 0.45 g/L. Dysmorphic red blood cells were also observed. Chest X-ray revealed extensive shadowing at the apex of the right lung, an oval shadow in the lower part of the left lung, and a nodular lesion at the apex of the left lung requiring further investigation with contrast-enhanced CT.

Pulmonology consultation was initiated, and a non-contrast CT revealed a polycyclic tumor (66×65×61 mm) in the upper lobe of the right lung with pleural involvement extending to the upper pole of the right hilum, and lymphangitic carcinomatosis-like changes around the tumor (Fig. 1).

Additionally, a polycyclic tumor (26×36×43 mm) was observed at the apex of the left lung, and a 9 mm nodule with lymphangitic carcinomatosis-like changes was present in the left lung (Fig. 2).

A small amount of fluid in both pleural cavities and enlarged lymph nodes in segments 1 and 2, as well as a 30×25 mm nodule in the left segment 6, were noted. Ultrasound of lymph nodes showed altered echogenicity in several left supraclavicular lymph nodes.

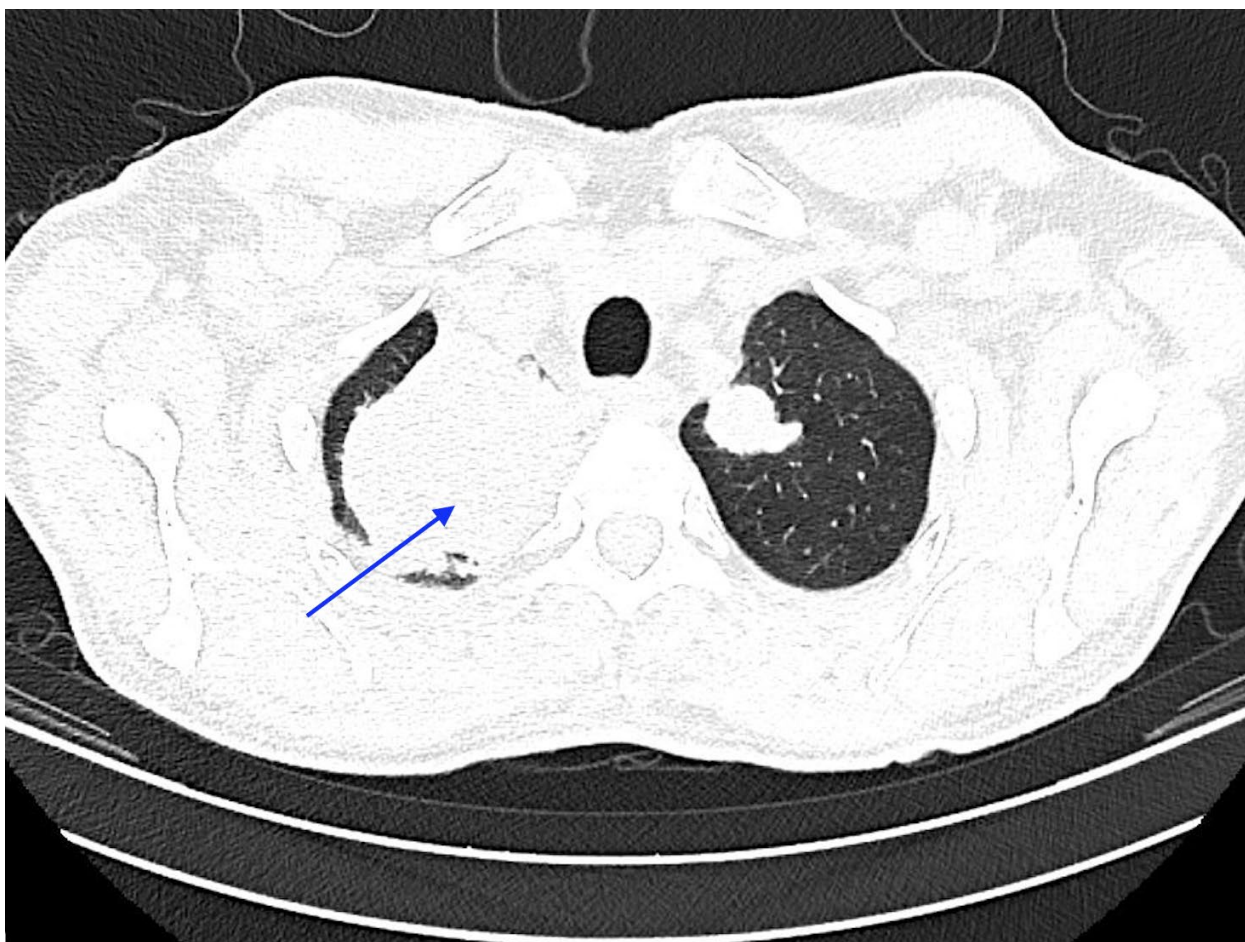


Fig. 1. CT of the chest with polycyclic tumor in the upper lobe of the right lung with pleural involvement

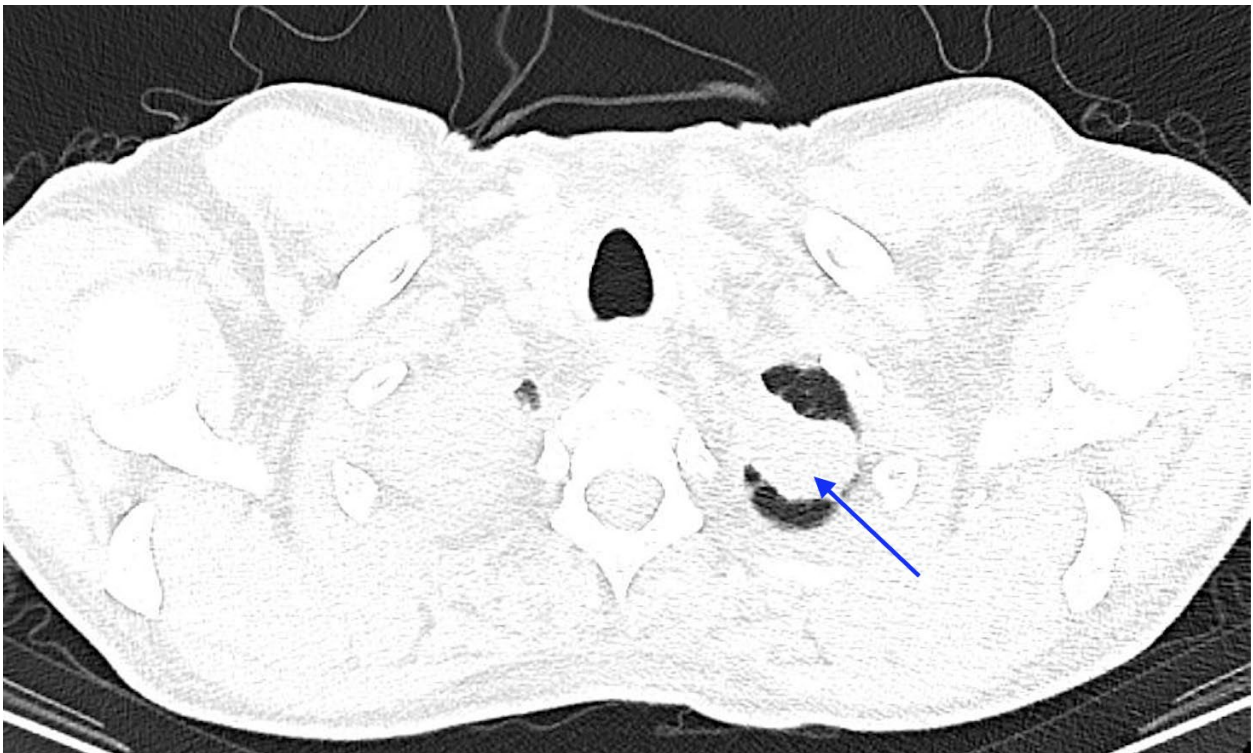
In-hospital treatment included intravenous hydration, broad-spectrum antibiotic therapy, allopurinol, painkillers, low-molecular-weight heparin adjusted to eGFR, and acetylsalicylic acid. Due to worsening anemia and the presence of fresh blood in the stool, acetylsalicylic acid was discontinued and 2 units of red blood cell concentrate were transfused. Furosemide was added to the therapy for lower limb edema, with a positive response. A rheumatology consultation led to the initiation of steroid therapy for suspected paraneoplastic syndrome-related bone and joint pain. A nephrology consultation was requested due to rising kidney parameters despite optimal conservative treatment and good diuresis. The patient was not deemed eligible for renal replacement therapy until metastatic spread of cancer was ruled out. A bronchoscopy was performed a week after admission, with no evidence of tumor cells in the material collected for general culture. However, a lymph node biopsy was recommended for histopathological examination, leading to an urgent referral to a highly specialized thoracic surgery department in case histopathological verification was needed.

Despite a high suspicion of cancer, a histopathological examination did not confirm the cancer hypothesis. Instead, positive results for ANCA antibodies and an-

ti-PR-3 antibodies were obtained, leading to suspicion of granulomatosis with polyangiitis. In early July, the patient was admitted to the clinic for confirmation of the diagnosis and initiation of treatment.

Upon admission, the patient was in good general condition but with dyspnea and lower limb edema. Bronchoscopy with EBUS was performed during hospitalization to definitively rule out cancer. Immunological tests revealed positive ANCA antibodies (1:160), positive anti-PR3 antibodies (28 IU/mL), while anti-MPO and anti-GBM were negative. Kappa and lambda light chains in serum were elevated in equal proportions. Levels of immunoglobulins IgA, IgG, IgM, and complement components C3 and C4 were normal. The final diagnosis was confirmed as granulomatosis with polyangiitis.

The worsening renal function necessitated hemodialysis, and a kidney biopsy was performed due to suspected secondary membranous nephropathy. The biopsy revealed features consistent with the late stage of proliferative extracapillary glomerulonephritis with crescents. Therapy with cyclophosphamide (CTX) at a dose of 1g, along with oral methylprednisolone at a dose of 32mg and prophylactic trimethoprim/sulfamethoxazole 480 mg, was initiated. A permanent catheter was implanted in the left internal jugular vein, and 7 plas-



**Fig. 2.** CT of the chest with polycyclic tumor was observed at the apex of the left lung

mapheresis procedures were performed during hospitalization. Two weeks after the first CTX pulse, the second pulse (900 mg) was administered, and anti-PR3 antibody levels were measured at 1.4 IU/mL. The patient was discharged after three weeks of hospitalization in a stable condition, appropriate for coexisting conditions, with ongoing recommendations until the results of the histopathological examination and immunological tests (ANA, ANCA, anti-GBM, and serum protein electrophoresis) were obtained. The histopathological examination did not confirm the cancer hypothesis, but positive results for ANCA antibodies and positive anti-PR-3 antibodies were obtained. Suspecting granulomatosis with polyangiitis, the patient was admitted to the clinic in early July for confirmation of the diagnosis and initiation of treatment. In addition to methylprednisolone and trimethoprim/sulfamethoxazole, the patient received metoprolol 25 mg, amiodarone 200 mg (both medications administered due to paroxysmal atrial fibrillation episodes observed in the ward), calcitriol 0.25 µg, calcium carbonate 1000 mg, and proton pump inhibitor 20 mg. Two weeks later, the patient was readmitted to the clinic for the administration of three pulses of cyclophosphamide (CTX) at a dose of 900 mg each and assessment of disease activity. Currently, the individual has completed five pulses of CTX (fourth and fifth doses also at 900 mg each) without complications, and the methylprednisolone dose is being gradually reduced.

## Discussion

The presented case outlines the complex diagnostic journey of a 52-year-old male who initially sought medical attention for a persistent dry cough and weakness, attributed to an upper respiratory tract infection. The patient's subsequent clinical course unfolded with atypical musculoskeletal symptoms, constitutional features, and unexplained laboratory abnormalities, prompting a multidisciplinary investigation. The initial therapeutic approach, combining levodropropizine and doxycycline, was chosen based on the presumptive infectious etiology. However, the persistence of symptoms and the emergence of systemic manifestations led to a comprehensive workup, revealing abnormal blood counts, elevated inflammatory markers, and deranged glucose metabolism.

Notably, the patient's history of smoking and excessive alcohol consumption raised concerns about potential contributing factors. The onset of the disease, starting with nonspecific symptoms of the upper respiratory tract, is common, yet it is not a specific symptom and may lull the doctor's vigilance.<sup>2</sup>

Subsequent evaluations, including imaging studies, unveiled pulmonary nodules and lymphangitic carcinomatosis-like changes. Weight loss, fever, and changes in lung imaging in a patient could suggest a developing neoplastic process. Various cases of initial suspicion of neoplastic disease are described before the diagnosis of GPA is established.<sup>26</sup> Despite initial suspicions of malignancy, the absence of tumor cells in bronchoscopic material and

the subsequent identification of specific autoantibodies underscore the challenges in distinguishing autoimmune conditions from neoplastic processes. The clinical presentation, coupled with positive anti-PR-3 antibodies, shifted the diagnostic focus towards GPA. The significance of renal involvement became apparent, necessitating hemodialysis and a kidney biopsy, ultimately confirming the presence of proliferative extracapillary glomerulonephritis. Plasma exchange was also used in this case to reduce the risk of end-stage cardiovascular disease in patients with acute primary disease.<sup>27</sup> Symptoms associated with renal failure in the form of nephritic syndrome are common, and biopsy is crucial in making the diagnosis of glomerulonephritis.<sup>28</sup> The initiation of a therapeutic regimen comprising cyclophosphamide, methylprednisolone, and supportive measures aimed to address both the vasculitic and renal components of GPA. The treatment strategy used is also described in other cases.<sup>27</sup> Prophylactic use of trimethoprim with sulfamethoxazole is important in the case of the applied therapy.<sup>29</sup>

The successful management of this patient, including the reduction of immunosuppressive therapy and stabilization of renal function, highlights the potential for favorable outcomes in GPA with prompt and targeted interventions. Continued follow-up, along with further investigations, including immunological markers and histopathological examinations, will be crucial for assessing treatment response and guiding ongoing care. This case contributes to the growing body of literature on atypical presentations of GPA, emphasizing the need for a holistic and dynamic approach in the evaluation and management of complex medical cases.

## Conclusion

In conclusion, the diagnostic odyssey of the 52-year-old male presented here illuminates the intricate challenges associated with identifying GPA, a formidable entity within the spectrum of autoimmune diseases. The patient's journey, from the initial presentation of seemingly benign symptoms to the ultimate confirmation of GPA, underscores the complexities involved in discerning this rare autoimmune disorder.

This case report serves as a poignant reminder of the multifaceted nature of GPA, characterized by protean clinical manifestations that can mimic other conditions, leading to diagnostic ambiguity. The hurdles encountered in the diagnostic process, exemplified by the patient's atypical musculoskeletal symptoms, constitutional features, and perplexing laboratory abnormalities, underscore the importance of a meticulous and collaborative approach in unraveling the intricacies of such autoimmune disorders.

Moreover, the diagnostic challenges highlighted in this report shed light on the broader landscape of GPA, emphasizing the need for increased awareness and im-

proved diagnostic capabilities. The evolving incidence patterns observed in recent decades, attributed partly to heightened awareness and advancements in diagnostic tools like ANCA testing, underscore the dynamic nature of our understanding of GPA.

This case not only contributes valuable insights into the diagnostic intricacies of GPA but also emphasizes the pivotal role of interdisciplinary collaboration in navigating such complex clinical scenarios. The successful management of the patient, with a tailored therapeutic approach targeting both vasculitic and renal components, serves as a beacon of hope, showcasing the potential for positive outcomes with timely and targeted interventions.

## Declarations

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### Author contributions

Conceptualization, P.S.; Methodology, L.S. and A.K.; Software, S.Z.; Resources, M.S. and A.B; Data Curation, P.S. and M.T.; Writing – Original Draft Preparation, P.S. and A.K.; Writing – Review & Editing, K.Ž. and K.K. and M.D.; Visualization, J.T.; Supervision, P.S.

### Conflicts of interest

The authors declare that there are no conflicts of interest regarding the publication of this article.

### Data availability

The datasets used and/or analyzed during the current study are open from the corresponding author on reasonable request.

### Ethics approval

Written informed consent for publication was obtained from the patient. We complied with the policy of the journal on ethical consent.

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