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Recognising Granulomatosis With Polyangiitis: A Case of Diverse Clinical Manifestations

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Abstract

Granulomatosis with polyangiitis (GPA) is an autoimmune syndrome, characterised by small- to medium-vessel vasculitis with associated extravascular necrotising granulomas. It is a rare systemic disease that typically affects the upper respiratory tract, lungs, and kidneys, although it can involve any organ. The rare presentation of GPA, combined with its wide range of potential manifestations, means that diagnosing it on first presentation can be challenging.

This case report details the diagnostic process of a 66-year-old woman who presented with non-specific symptoms. Her presentation was initially thought to be non-resolving pneumonia, and she received a prolonged course of broad-spectrum antibiotics; however, she remained unwell with high inflammatory markers. Her case was discussed with a variety of clinical specialities, and the possibility of GPA was initially refuted because anti-proteinase 3 (anti-PR3) levels were only mildly raised. The outcome of a multidisciplinary team meeting was that a lung tissue biopsy would be required for diagnosis; however, by this point, the patient had become more unwell and was no longer fit for a lung biopsy. The decision was therefore made to transfer her to a renal centre, where a renal biopsy could be performed, which showed focal crescentic glomerulonephritis, in keeping with a diagnosis of GPA. She received IV steroids and cyclophosphamide and is now under the care of the renal team. This case report highlights the challenges associated with diagnosing a rare disease with a vague presentation and the role that the multidisciplinary team plays in the diagnostic pathway.

Categories: Rheumatology, Pulmonology, Nephrology
Keywords: canca/proteinase 3 (pr3)-positive granulomatosis, diagnostic delay, granulomatosis with polyangiiitis, mdt collaboration, wegener's granulomatosis

Introduction

Granulomatosis with polyangiitis (GPA) is an autoimmune syndrome, characterised by small- to medium-vessel vasculitis with associated extravascular necrotising granulomas. It is a systemic disease that typically affects the upper respiratory tract, lungs, and kidneys, although it can involve any organ. GPA is a rare disease, with an incidence of 11.8 per million person-years [1]. The rare presentation of GPA, combined with its wide range of potential manifestations, means that diagnosing it on first presentation can be challenging. A delay in diagnosis of GPA can lead to a delay in the initiation of immunosuppressive therapy, which has been associated with higher rates of organ-threatening complications and mortality [2]. It is therefore important to recognise the role of investigations that may be used in the diagnostic process.

The challenge of diagnosing GPA is created by its non-specific presentations, a range of clinical and radiological mimics, and a lack of standardised diagnostic criteria. As GPA treatment relies on immunosuppressive therapy, it is therefore especially important to exclude infectious mimics or coinciding infections that may contribute to the patient's presentation. One particular infectious mimic is tuberculosis, which can also present with cavitating lung lesions.

One biomarker typically used to aid diagnosis is serum cytoplasmic antineutrophil cytoplasmic antibody (c-ANCA), which has been reported to be positive in over 75% of GPA cases [3]. ANCA, however, can be positive in other conditions [4], and the positive predictive value of ANCA positivity can be lower in patients who have GPA localised to the respiratory system [5]. ANCA therefore cannot be relied upon in isolation for the diagnosis of GPA. Tissue biopsy is an ideal contributor to GPA diagnosis; however, this presents a potential cause for delay in diagnosis, and treatment may need to be initiated prior to biopsy [6]. Biopsies are also associated with procedure-related risks to the patient.

This case report details the diagnostic process of a 66-year-old woman presenting with diverse non-specific symptoms, which was initially misdiagnosed as unresolved pneumonia. This led to a prolonged hospital admission, which ultimately led to the identification of GPA.

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Case Presentation

A 66-year-old lady with a past medical history of hypertension and atrial fibrillation (ablated 10 years prior) presented to her GP with a one-week history of cough and breathlessness. Her GP started her on amoxicillin for treatment of a lower respiratory tract infection (LRTI). However, the following day, she measured her observations at home and noted her oxygen saturations to be 87%, so she attended her local Accident & Emergency (A&E) Department. Blood tests revealed a raised C-reactive protein (CRP), and a chest X-ray (CXR) revealed widespread nodular opacities (Table *1* and Figure *1*). She was treated for bilateral community-acquired pneumonia (CAP) and discharged home from A&E with azithromycin added to her antibiotic regimen and a plan for an outpatient follow-up CXR.

Parameter	Value on initial A&E presentation	Value on repeat presentation (5 weeks later)	Value after 2 weeks in hospital	Value 6 months after immunosuppression	Lab reference range	Units
Hb	113	112	87	108	115-165	g/L
MCV	88.9	85.1	84.9	94.8	80-100	fL
WCC	9.32	16.42	12.96	6.79	4-11	109/L
Platelets	428	718	1041	276	150-450	109/L
Neutrophils	6.43	13.46	10.43	4.89	2-7.5	109/L
CRP	67	168	114	4	0-5	mg/L
Sodium	134	132	129	130	133-146	mmol/L
Potassium	4.2	4.5	4.3	4.5	3.5-5.3	mmol/L
eGFR	>90	>90	>90	55	>90	mL/min/1.73 m^2
Bilirubin	-	8	6	5	0-21	µmol/L
Alkaline Phosphatase	-	89	187	83	30-130	IU/L
Alanine Transaminase	-	35	11	16	0-34	IU/L

TABLE 1: Serial Laboratory Results

Blood results shown from initial presentation, re-presentation five weeks later, after two weeks of antibiotics and six months after immunosuppression.

Hb, Haemoglobin; MCV, Mean Cell Volume; WCC, Total White Cell Count; CRP, C-reactive Protein; eGFR, estimated Glomerular Filtration Rate



FIGURE 1: Chest X-ray on Initial A&E Presentation

A&E, Accident & Emergency

Five weeks later, she re-presented to the Emergency Department with palpitations and a fever of 38.5°C. She was found to be in atrial fibrillation with a fast ventricular response and hypotension, for which she received electrical cardioversion.

On further questioning, she reported that she had been feeling generally unwell and fatigued for a total of 10 weeks before developing a dry, non-productive cough and intermittent fevers. She denied haemoptysis, weight loss, or other constitutional symptoms. She had no significant travel history or known exposure to a notifiable disease. On auscultation of her chest, crepitations were heard bilaterally, scattered throughout the middle and upper lung zones. She had no cutaneous manifestations of disease.

A CXR was performed, which revealed an interval increase in the density of the bilateral consolidation (Figure *2*). Her blood tests showed that her CRP had risen even higher, and she now had elevated neutrophils, although her renal function remained stable (Table *1*). She was therefore admitted to the respiratory ward for treatment of non-resolving CAP with IV antibiotics, as well as supplemental oxygen.

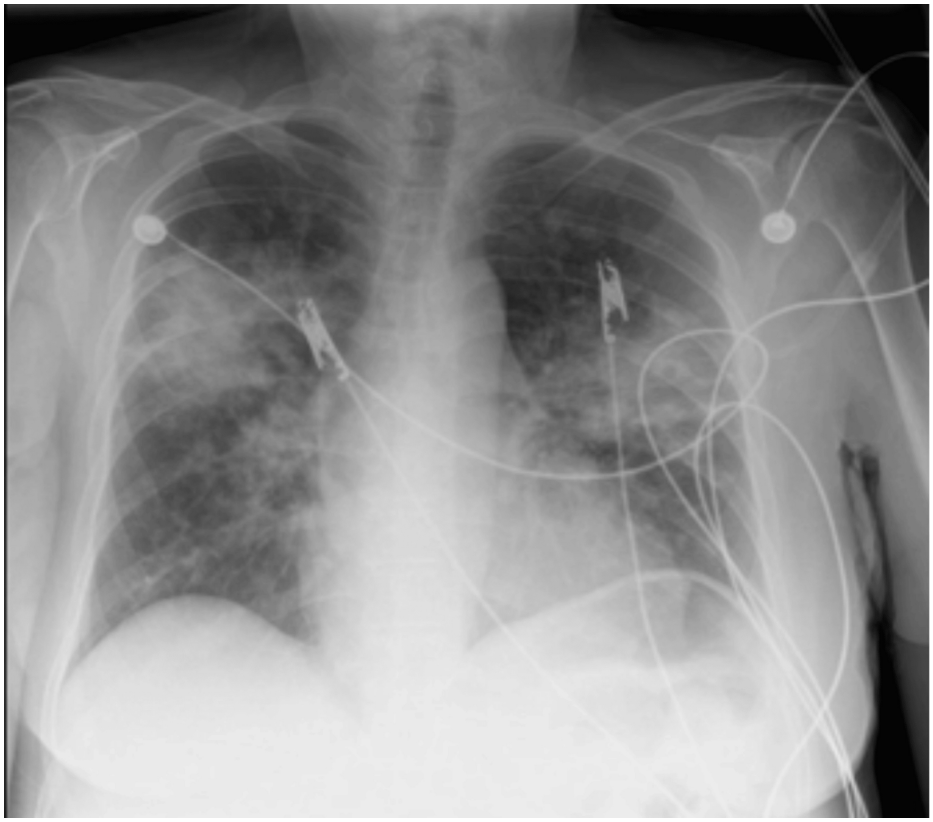


FIGURE 2: Chest X-ray on Repeat Presentation

A computed tomography (CT) thorax was performed due to the non-resolving and unusual appearance of her CXR, which was initially reported to show interval development of an extensive bilateral, perihilar, confluent consolidative mass lesion (Figure *3*). This confluence spared the peripheries and predominantly affected both upper and middle lung lobes, along with multiple scattered patches of air-space opacification in the right lower lung and a mild right-sided pleural effusion. In view of the clinical history, this was initially reported to likely reflect an infective aetiology, although the treating team did not feel that this was purely infection.

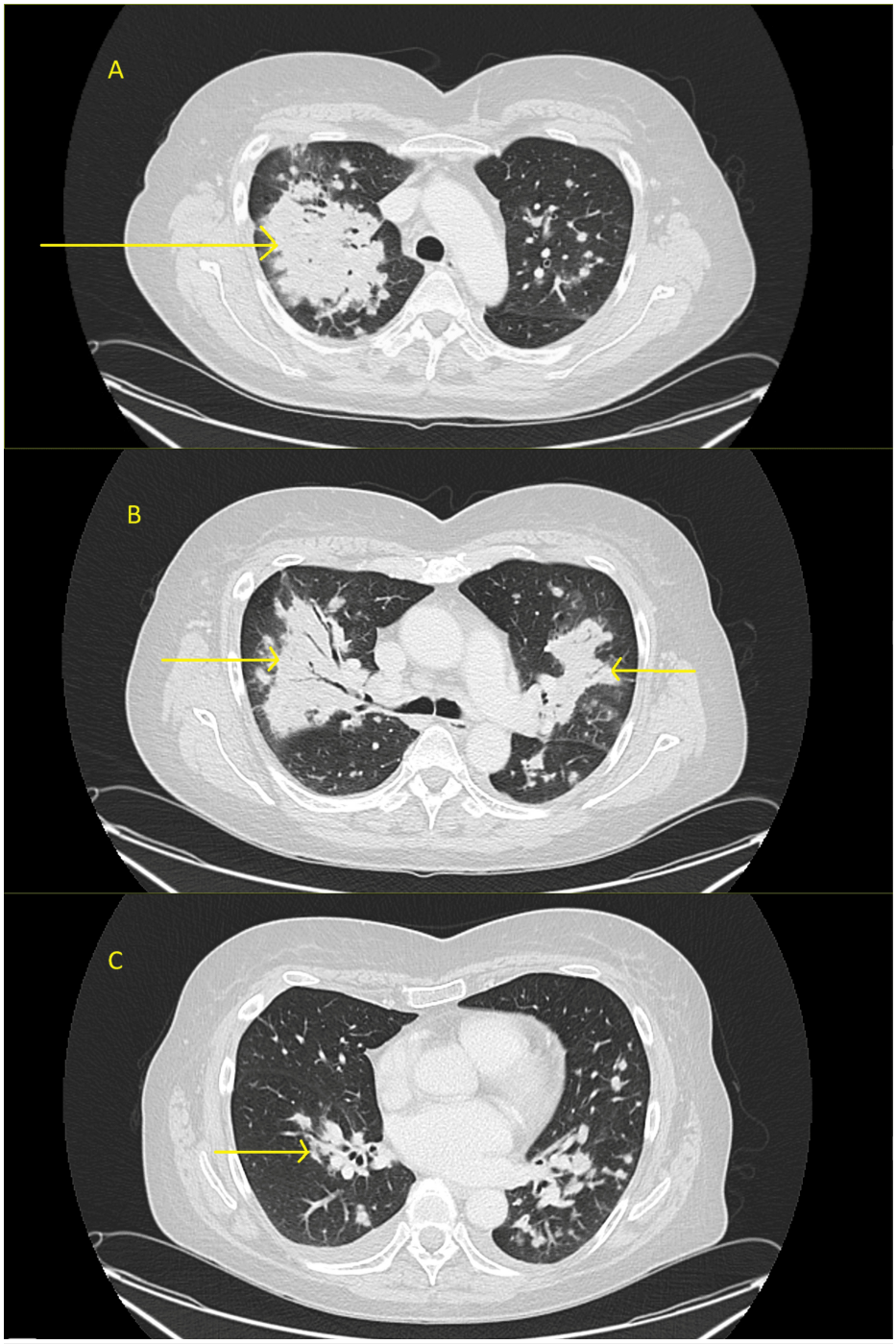


FIGURE 3: Slices From CT Thorax

Panel A: Axial image at the level of T3/T4, with an arrow pointing towards an area of consolidation in the right upper lobe with peripheral sparing.

Panel B: Axial image at the level of the carina (T5-T6), with arrows pointing towards areas of perihilar consolidation in the right and left lungs.

Panel C: Axial image at the level of T6/T7, with an arrow pointing towards an area of air-space opacification scattered throughout the right lower lobe.

CT, Computed Tomography

To further investigate the underlying aetiology, a full infective respiratory screen was sent, including sputum cultures, an extended respiratory viral panel, and an atypical pneumonia screen. All of these results were negative. A CT scan of her abdomen revealed no intra-abdominal source of infection, and an

echocardiogram revealed no indication of infective endocarditis.

Bronchoscopy revealed petechiae on the mucosa of her lower trachea, extending into the left upper and lower lobes, as well as the right lower lobe. Easy contact bleeding was noted around the upper lobe segments, with some airway narrowing limiting the ability to pass the scope into the right upper lobe. Bronchoalveolar lavage samples returned negative for bacterial and fungal cultures. Two separate sputum samples and two bronchoalveolar lavage samples were all negative for acid-fast and alcohol-fast bacilli. These four samples were all sent for tuberculosis culture.

After 10 days of broad-spectrum IV antibiotics, she remained clinically unwell, with an ongoing oxygen requirement, raised inflammatory markers, and intermittent runs of fast atrial fibrillation. Over this timeframe, she was noted to have progressive normocytic anaemia and thrombocytosis, and an electrolyte panel at this time showed she had developed hyponatraemia. She had also developed a mildly raised alkaline phosphatase (Table *1*). Procalcitonin at that time was 0.09 µg/L (reference range <0.05). This value was not deemed to be significantly raised, suggesting bacterial infection was not the likely pathology.

Further investigation for involvement of other organ systems found that estimated glomerular filtration rate (eGFR) remained stable, although she had developed haematoproteinuria, with a raised urine protein-to-creatinine ratio of 81 (reference range 0-15) and urine microscopy positive for red cells.

An autoimmune screen revealed a positive cANCA, with an anti-PR3 antibody titre of 4.8 IU/mL (reference range: <2 IU/mL). Other antibodies, such as pANCA (anti-myeloperoxidase (anti-MPO)), antinuclear antibodies, anti-extractable nuclear antigen (anti-ENA) and anti-glomerular basement membrane (anti-GBM) antibodies, were all within the normal range. This raised suspicion of GPA, prompting a CT scan of the sinuses to assess her upper respiratory tract. This revealed chronic sinusitis. She also underwent a renal tract ultrasound, which revealed normal appearance of the renal parenchyma. On examination, there were no cutaneous manifestations of the disease, such as a rash or saddle-nose deformity.

There were several discussions with multiple teams throughout her inpatient admission. Her CT images (Figure *3*) were rediscussed and reviewed by a specialist chest radiologist, who noted that there were small areas of cavitation within the upper lobe consolidation, as well as small foci of central cavitation within the peripheral nodular opacities. Her history and investigations were discussed with a rheumatologist, who advised that the mildly raised anti-PR3 was unlikely to represent a rheumatological pathology and recommended not initiating steroid therapy until a diagnosis was confirmed. Her results were also discussed with the renal team, who initially had no concerns due to normal renal function; however, following an in-person review of the patient, they agreed that the aetiology was likely vasculitis. All teams agreed that a tissue biopsy would aid diagnosis. The patient was therefore discussed at the regional interstitial lung disease multidisciplinary team (MDT) to consider a potential lung biopsy for further characterisation of the parenchymal changes seen on CT imaging.

Initially, the MDT recommended a renal biopsy, as it was felt to have a lower associated risk than a lung biopsy. However, the renal team felt that a renal biopsy would be of limited diagnostic yield, given the normal imaging appearances of the kidneys, stable renal function, and only mild proteinuria. A lung biopsy was therefore arranged, with the aim of performing a CT-guided biopsy locally. However, by this point, her anaemia had progressed such that she was requiring blood transfusions to maintain an Hb over 70, and it was felt that she would not be safe for a lung biopsy.

She was therefore ultimately transferred to a renal centre for renal biopsy, which revealed that 6 of the 25 glomeruli biopsied showed pauci-immune crescents (five cellular and one fibrous). Four of these cellular crescents were associated with fibrinoid necrosis. One glomerulus showed segmental fibrinoid necrosis without crescent formation. There was also acute tubulointerstitial nephritis with many eosinophils. At least one large artery showed fibrinoid necrosis. These features are consistent with pauci-immune focal crescentic glomerulonephritis. Unfortunately, the patient suffered a bleed post-biopsy, which resulted in a transient deterioration in renal function.

In view of her renal biopsy findings, clinical history and mildly raised serum anti-proteinase 3 (anti-PR3) antibody, the vasculitis MDT determined the most likely diagnosis was GPA, and the decision was made to start standard induction therapy with IV steroids, cyclophosphamide and rituximab. Her respiratory symptoms improved, and she was quickly weaned off supplemental oxygen. She was then discharged from hospital with a prolonged weaning course of oral prednisolone.

She was followed up in a joint respiratory and renal clinic as an outpatient. Her sputum and bronchoalveolar lavage samples had now all returned, showing no mycobacterium species isolated after eight weeks. An interferon gamma release assay test was also performed, which was negative.

Her respiratory symptoms improved with this treatment, and a follow-up thoracic CT scan six weeks later showed interval improvement of the consolidative changes, with residual fibrotic changes. A CXR six months after treatment showed resolution of the previously demonstrated bilateral consolidation, with

some residual areas of post-inflammatory fibrotic changes (Figure *4*). Blood tests at this time showed her inflammatory markers had also normalised (Table *1*). Urine protein-to-creatinine ratio had also normalised at this time, showing proteinuria had resolved as well.

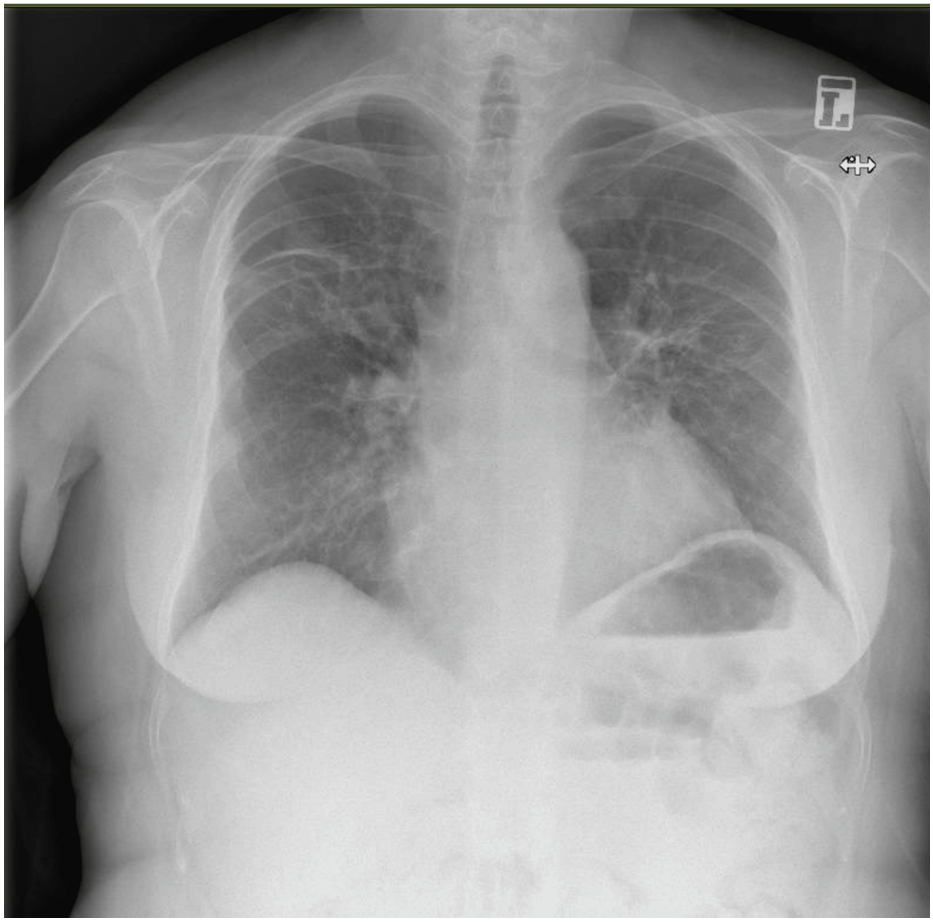


FIGURE 4: A CXR Six-Months Post-treatment

CXR, Chest X-ray

Discussion

GPA is a systemic vasculitis, formerly known as Wegener's granulomatosis. GPA is a small-to-medium vessel vasculitis associated with the formation of necrotising granulomas. This process typically involves tissues in the upper respiratory tract, lungs, and kidneys, although it can affect any organ. In addition to the symptoms associated with specific organ involvement, many patients suffer from constitutional symptoms such as fatigue, myalgia, weight loss, and fevers.

GPA is classified as a rare disease, with an incidence of 11.8 cases per million person-years in the UK and a prevalence of 138 per million [1]. Recognising and diagnosing a first presentation of GPA can be challenging due to its low incidence rate and wide range of clinical manifestations. This case outlines the protracted diagnostic process for a first presentation of GPA, which was made challenging by the non-specific symptoms, laboratory results, and imaging results. This diagnostic challenge was compounded by interdisciplinary disagreements on the optimum investigation and management strategies.

Delayed diagnosis and treatment of GPA have been shown to be associated with worse outcomes, including increased rates of mortality or irreversible organ damage [2]. This highlights the importance of a diagnostic pathway that promotes early recognition and investigation, allowing treatment to be initiated in a timely manner.

A characteristic biomarker that can aid the diagnosis of GPA is the presence of ANCA. On reviewing the main types of ANCA antibodies, it has been reported that at least 75% of GPA cases are positive for anti-PR3 antibodies, with 10% positive for anti-MPO antibodies and 10% of cases negative for all ANCAs [3]. The rates of ANCA positivity, however, are lower in cases of localised GPA, where disease activity is confined to the respiratory tract [5]. This highlights that ANCA positivity alone cannot be used to confirm or refute a

diagnosis of GPA. The diagnosis of seronegative GPA can be particularly challenging and may rely on tissue biopsy, which creates an additional procedure-related risk to the patient.

In this case, the diagnosis was initially refuted due to the interpretation that the anti-PR3 level was only mildly elevated in comparison to the patient's disease severity and significantly raised inflammatory markers. Whilst it has been reported that a higher ANCA titre is associated with a greater positive predictive value for vasculitic conditions [4,7], the existence of ANCA-negative GPA means that the antibody level cannot be interpreted in isolation as part of the diagnosis.

To our knowledge, there are currently no standardised diagnostic criteria for GPA in the UK. In 1990, the American College of Rheumatology (ACR) created criteria that assess the presence of abnormal urine sediment (red cell casts or red cells seen on microscopy), abnormal findings on chest imaging (nodules, cavities, or infiltrates), oral ulcers or nasal discharge, and granulomatous inflammation on biopsy. The presence of haemoptysis was also included as a criterion in a classification tree produced by the ACR. The presence of two or more of these features was associated with a sensitivity of 87% and a specificity of 93% [8]. These criteria, however, were primarily created as a tool for disease classification in research rather than for clinical diagnosis. Their current use in a clinical environment is limited, as they were developed prior to the widespread availability of ANCA testing and CT imaging. A reappraisal of the 1990 criteria found a much lower positive predictive value when they were used as a diagnostic tool in a patient population [9].

In 2022, a joint effort by the ACR and European Alliance of Associations for Rheumatology produced updated criteria that can be used to classify a diagnosed ANCA-associated vasculitis as either GPA, microscopic polyangiitis, or eosinophilic GPA [10]. These criteria included an interpretation of ANCA serotyping to further develop the classification of vasculitis as GPA, although they do not serve as initial diagnostic criteria.

This case highlights the role of specialist regional centres in discussing potential investigations and management strategies for rare diseases. GPA can be especially challenging to diagnose in the context of a smaller district general hospital. The low disease incidence means that clinicians are less likely to have exposure to this patient population and may be less likely to recognise a non-specific presentation. The lack of standardised diagnostic criteria and reliance on specialist diagnostic procedures, such as tissue biopsy, further compound the diagnostic challenges in these cases. This highlights the importance of involving specialists within an MDT who can facilitate a diagnostic pathway for these patients.

Conclusions

In summary, this case serves to highlight that GPA is a differential diagnosis in patients with non-specific symptoms and raised inflammatory markers. Seropositivity for ANCA subtypes cannot always be relied upon, and tissue biopsy offers useful diagnostic insight, although it is associated with further risk to the patient. MDT input is beneficial in such cases, as specialist input can offer alternatives to the initially proposed diagnostic pathway.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Oliver R. Brady, Asad Anwar

Acquisition, analysis, or interpretation of data: Oliver R. Brady, Asad Anwar

Drafting of the manuscript: Oliver R. Brady, Asad Anwar

Critical review of the manuscript for important intellectual content: Oliver R. Brady, Asad Anwar

Supervision: Asad Anwar

Disclosures

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