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A Case of Granulomatosis with Polyangiitis with Positive Atypical-ANCA

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Abstract

Granulomatosis with polyangiitis (GPA) is a rare primary systemic vasculitic condition, affecting small to medium sized vessels. It is associated with a raised anti-neutrophil cytoplasmic antibody (ANCA) count with diagnosis confirmed via histological findings. This report is centered on a rare occurrence of pulmonary GPA in an 80 year-old female patient with a, elevated atypical ANCA level.

Keywords: Granulomatosis; Polyangiitis; Anti-neutrophil cytoplasmic antibody

Introduction

Granulomatosis with polyangiitis (GPA) is a subtype of systemic vasculitides, often proving difficult to diagnose due its variety of clinical presentations. These can range from respiratory complaints, to dermatological or ophthalmological manifestations, depending on the location of the blood vessels affected [1]. GPA is commonly associated with an elevated anti-neutrophil cytoplasmic antibody (ANCA) count; with cytoplasmic ANCA (C-ANCA) raised in 80-90% of patients and perinuclear-stained ANCA (P-ANCA) elevated in 10% [2]. The patient being discussed in this report is an 80-year-old female who presents with a rare case of pulmonary GPA. When investigated she was found to have a raised atypical ANCA with negative C-ANCA and P-ANCA levels.

Case Report

The patient being presented is an 80-year-old female, with a past medical history of atrial fibrillation, hypertension, gastro-oesophageal reflux disorder (GORD) and breast cancer. She presented to a rural hospital with increasing shortness of breath, a productive cough and intermittent fevers which had been ongoing for two weeks. Initially treated for a suspected pneumonia, the patient was prescribed intravenous fluids and treated with Ceftriaxone and Doxycycline. Despite this, her shortness of breath worsened and she had an increasing oxygen requirement with saturations of just 92% while on six litres of oxygen via nasal prongs. Her antibiotic regime was later altered to consist of Meropenem and Azithromycin, and she was transferred to our hospital for further management.

Upon arrival in the emergency department, she was noted to have ongoing shortness of breath with a respiratory rate of 33 breaths per minute and oxygen saturations of 97% on six litres of oxygen. Her blood pressure was stable at 132/105, her temperature was 38 degrees celsius, she was tachycardic at 115 beats per minute and her pulse was irregularly irregular. On examination, she had left basal crepitations, but otherwise exhibited no signs of respiratory distress and was haemodynamically stable. She was initially managed with 10 litres of oxygen via a Hudson's mask, nebulised Salbutamol, IV frusemide and her electrolytes were optimised. Her investigations showed an elevated white cell count of 20, a potassium level of 2.7, a creatinine of 104 and an estimated GFR of 44. She also tested positive for Influenza A RNA and a chest X-ray revealed left lower zone consolidation suggestive of a left lower lobe pneumonia (Figure 1A).

Due to worsening shortness of breath, she was placed on high flow nasal prongs at 40L/minute with an FiO_2 of 0.40 and was admitted to the high dependency unit (HDU) for management of Influenza A pneumonia, complicated by type 1 respiratory failure requiring non-invasive ventilatory support. On day five of admission, following improvement of her respiratory symptoms,

she was stepped down to the medical ward for ongoing management and was discharged 2 days later.

Following discharge, she was reviewed in the respiratory outpatient clinic, where she complained of persistent productive cough and as a result she underwent a CT scan of her chest. This revealed a large left lower lobe lesion, initially raising concerns of a lung malignancy, particularly in the context of her past history of right breast cancer (Figure 1B). She then underwent a CT-guided core biopsy to characterize the lesion, which showed a necrotising granulomatous inflammation with no evidence of malignant cells (Figure 1C). The differential diagnoses considered for this lesion included: malignancy, a lung abscess following her influenza infection, tuberculosis, a pulmonary fungal infection and finally autoimmune conditions including sarcoidosis and GPA. A bronchoscopy was performed and an endobronchial biopsy was negative for malignancy and there was no evidence of fungal elements or acid-fast bacilli (AFB) on bronchoscopy washings (Figures 1D and 1E). Further investigations revealed a raised C - reactive protein (CRP) of 6.9, an atypical ANCA level of more than 2560, a negative P-ANCA, a negative C-ANCA, and negative Angiotensin-Converting Enzyme (ACE).

Based on her clinical presentation, positive ANCA level, and histological evidence, she was diagnosed with GPA. A pulmonary function test was performed which showed mild airflow limitation, small airway obstruction with gas trapping, and a mild decrease in the corrected diffusion deficit, which is consistent with an interstitial lung disease pattern. She was given oral prednisolone 25 mg daily, oral methotrexate 5mg weekly and oral folic acid 0.5mg daily. On review in clinic two weeks later, her persistent cough resolved.

Discussion

Vasculitides are a diverse group of autoimmune diseases, characterized by blood vessel wall inflammation and a subsequent impediment of oxygen delivery to affected organs, causing ischemia and damage [3]. GPA, formerly known as Wegener's granulomatosis, is a rare pauci-immune member of the vasculitides family, which predominantly affects small and medium-sized vessels [4-6].

Epidemiologically, it has a higher incidence in Europe (up to 14.3 cases/million people) in comparison to Asian countries (2.1 cases/million) [7]. Although it can present in any age group, it is most commonly diagnosed in adults from 40 to 70 years old (with a peak incidence in the group over 55) and exhibits no specific gender preference [7,8]. The pathogenesis of GPA is not well understood, however, it is believed that there are genetic associations with HLA-DPB1*0401, RXRB, RING, SEMA6A and SERPINA, all of which have been found in affected individuals [9,10]. Some known triggers for GPA include infection, environmental exposures and some drugs.

GPA is associated with varied clinical presentations primarily consisting of organ-damage specific to the location of vessel wall injury. In a report by Comarmard and Cacoub, two clinical phenotypes of GPA were identified; limited and systemic forms [6]. The localized type predominantly presents as recurrent respiratory tract infections and is associated with a Th1 lymphocytic response, coupled with granuloma formation visualised on histology [6]. The systemic variant typically has a more severe presentation and may involve the kidneys or other vital organ systems, resulting in musculoskeletal, visual, dermatological or neurological complaints (Table 1) [1,3,6,11-20]. Patients affected by the systemic form of GPA develop constitutional symptoms such as fever, weight loss, night sweats, fatigue and arthralgia [5]. It is associated with a predominant Th2 lymphocytic response and is noted to demonstrate vasculitic lesions on histology [6].

Table 1: *Clinical presentation of GPA.*

	History	Physical Examination	Ref:
Respiratory	• Upper respiratory tract: nasal congestion/discharge, nose bleeds, sinus tenderness. • Lower respiratory tract: cough, haemoptysis, shortness of breath. • Other symptoms: Chronic cough, pleuritic chest pain.	• Purulent or bloody nasal discharge • Saddle nose deformity • Respiratory distress • Decreased breath sounds, inspiratory crepitations • Hypoxia with respiratory failure	[1,5,6,12-15]
Renal	• Fatigue • Frothy urine	• Proteinuria on dipstick examination	5,13,15
Dermatological	• Skin rash	• Palpable purpura • Tender subcutaneous nodules • Ulcers	1,3,16
Rheumatological	• Joint pain • Muscle aches	• Muscle weakness	1,6,17

Neurological	• Chronic headache • Ataxia • Seizures • Impaired motor and/or sensory function	• Cranial and peripheral nerves deficits	5,14,15,18
Auditory	• Hearing loss	• Middle ear swelling, erythema and effusion • Conductive hearing loss	12,15,19
Visual	• Eye erythema and pain • Foreign body sensation • Blurred vision	• Cataracts • Diplopia • Conjunctival hyperemia • Episcleritis • Scleritis	1,5,14,20
Cardiac	• Chest pain • Arrhythmias	• ECG abnormalities • Features of heart failure	14,15,19
Constitutional	• Fever • Malaise • Anorexia • Lethargy	• Fevers • Weight loss	12,15,19

A well-known classification system for the identification of GPA is the American College of Rheumatology (ACR) classification criteria which mandates the patient fulfilling of at least two of the four criteria for diagnosis. The criteria include: 1) the presence of nasal or oral inflammation; 2) radiographic abnormality; 3) abnormal urinary sediment on urinalysis; 4) histological evidence of granulomatous inflammation [18].

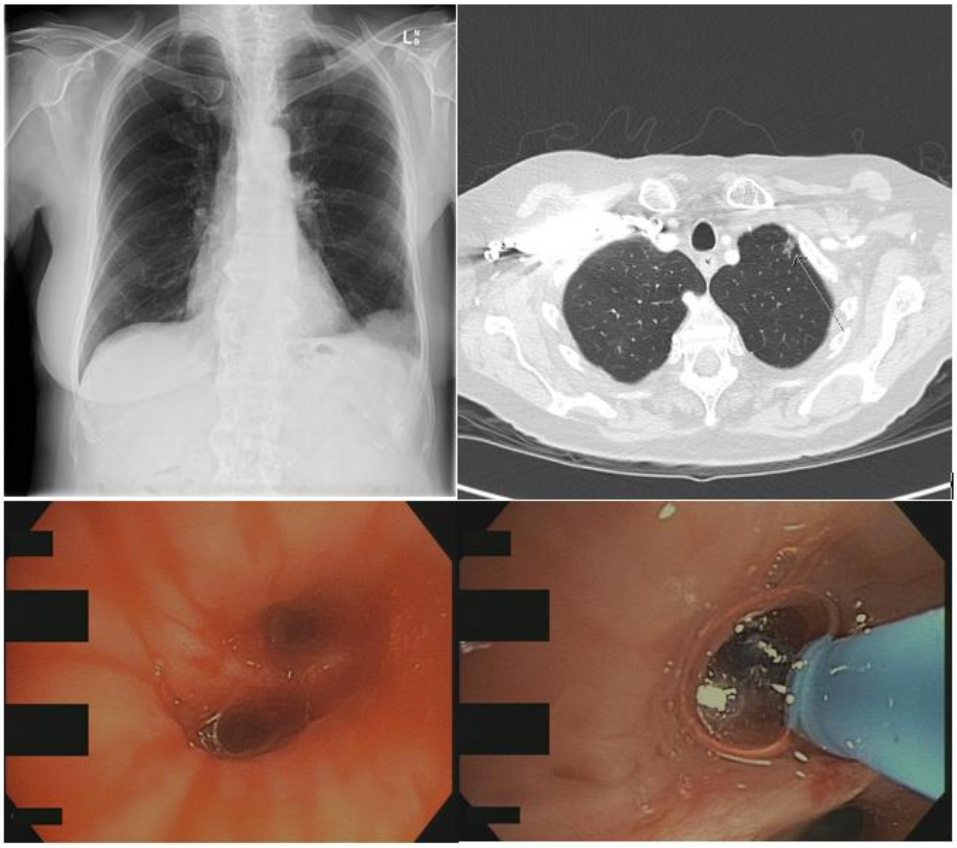
When performing investigations, it is important to consider laboratory testing, imaging and histology (Table 2).

Table 2: *Investigations for GPA.*

Test	Components	Findings	Significance
CBE	White cell count	Elevated white cell count	Inflammation
	Haemoglobin	Normocytic-normochromic anemia	Anaemia of chronic disease, or, reduced EPO function secondary to kidney disease
	Platelets	Elevated platelet count	Inflammation
EUC	Urea, Creatinine	Normal	Kidneys not affected
		Elevated	May suggest renal involvement
	eGFR	Current renal function	Baseline renal function and for prognostication
	Electrolytes	Normal or Deranged	Affected electrolytes secondary to renal involvement
Inflammatory markers	CRP, ESR	Elevated	Inflammation
Autoimmune Screen	ANCA	Positive or Negative • PR3-ANCA or C-ANCA (common) • MPO-ANCA or P-ANCA (less common)	Positive suggests GPA, MPA, EGPA or inflammatory bowel disease
	ANA	Negative	To assess for differential diagnoses
	RF	Negative	To assess for differential diagnoses
Imaging	CXR	Pulmonary nodules, consolidation, or effusion	To assess for pulmonary involvement and determine progression of disease
	CT Chest	Ground-glass opacity and consolidation	Diffuse alveolar haemorrhage
		Septal thickening	Resolving phase following diffuse alveolar haemorrhage
		Subglottic trachea narrowing	Suggestive of tracheal involvement
		Pleural effusion, nodules or thickening	Suggestive of pleural involvement
Urine	Urinalysis	Dysmorphic RBCs, RBC casts and/or WBC casts, urinary sediment	To assess for glomerular disease and determine progression
Histology	Biopsy of affected tissue	1. Granulomatous inflammation 2. Necrotising vasculitis	Definitive diagnosis for GPA

*ANA: antinuclear antibody, ANCA: antineutrophilic cytoplasmic antibodies, CBE: complete blood examination, CRP: C-reactive protein, CXR: chest X-ray, eGFR: estimated glomerular filtration rate, EGPA: eosinophilic granulomatosis with polyangiitis, EPO: erythropoietin, ESR: erythrocyte sediment ratio, EUC: electrolytes, urea and creatinine, MPA: microscopic polyangiitis, MPO: myeloperoxidase, PR3: proteinase 3, RBCs: red blood cells, RF: rheumatoid factor.

Figure 1: *A: Chest X-ray showing left lower zone consolidation suggestive of a left lower lobe pneumonia; B: CT Chest demonstrating a triangular opacity in the left lower lobe measuring 51 x 33mm with vessels present within it and a central area of necrosis measuring 18 x 21mm corresponding with the previous CXR findings; C: Gathering histological samples of the left lower lobe CT-guided core biopsy showing necrotising granulomatous inflammation; D: Biopsy of left lower lobe lesion on Bronchoscopy; E: Post-biopsy bleed on Bronchoscopy.*



Routine laboratory testing should include a complete blood count, erythrocyte sedimentation rate (ESR) and CRP to assess for features of inflammation [8,16]. A specific autoimmune panel also includes ANCA, which is a good screening test for small vessel necrotising vasculitis, including GPA, microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA) [12]. A positive ANCA can be one of 3 types: cytoplasmic, perinuclear or atypical. A recent study on GPA patients concluded that 85% were C-ANCA positive, 10% were P-ANCA positive, and 5% were ANCA negative [14]. Atypical ANCA is rarely seen in patients with systemic small-vessel vasculitis, but has been reported in hepatobiliary diseases including chronic inflammatory bowel disease, primary sclerosing cholangitis, primary biliary cirrhosis and autoimmune hepatitis [12,22-23]. Other autoimmune screening tests include antinuclear antibody (ANA), rheumatoid factor (RF) and ACE which can aid in excluding other differential diagnoses [12,19].

Recommended imaging assessment includes a chest radiograph for a baseline image and to monitor disease progression. Additionally, a CT scan of the chest may better elicit the severity of disease and aid as a guide for biopsy and/or intervention purpose [16,24].

Histological assessment of GPA is the gold-standard investigation. There are two predominant histological patterns seen in this condition: necrotic granulomatous inflammation and vasculitic inflammation [17]. The case discussed above depicts the localized form of GPA whereby our patient presented with ongoing respiratory symptoms, an elevated atypical ANCA level and a histological finding of necrotising granulomatous inflammation.

The mainstay of treatment for GPA is steroids and immunosuppressive agents. For the induction of remission, immunosuppressive agents including cyclophosphamide or methotrexate, and monoclonal antibodies such as Rituximab are commonly used [25,26]. Current guidelines suggest that the maintenance therapy duration should be at least 2 years at which time the patient should be reassessed to determine whether treatment cessation is appropriate [26].

Conclusion

In conclusion, this report has focused on a patient who, following an Influenza A pneumonia, presented with persistent respiratory symptoms for more than two months duration. Following investigation with laboratory testing, imaging and histological assessment, it was concluded that the patient had an atypical ANCA-positive GPA. On reviewing articles and case reports previously conducted on this topic, it is understood that this patient's condition, which involved only her respiratory system and spared all other organs, is very rare. The patient was successfully treated following prompt assessment and management with steroids and immunosuppressive agents.

Guarantor of Submission

The corresponding author is the guarantor of submission.

Source of Support

None

Consent Statement

Written informed consent was obtained from the patient for publication of this case report.

Conflict of Interest

Authors declare no conflict of interest.

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