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# Granulomatosis with Polyangiitis (GPA), an Important Differential Diagnosis in Sepsis

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***Authors' contributions***

*This work was carried out in collaboration between all authors. Author DL wrote the draft of the manuscript. Author PC managed the literature searches. Author DL designed the figures, managed literature searches and contributed to the correction of the draft. Author SRV provided the case, the figures and supervised the work. All authors read and approved the final manuscript.*

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***Case Report***

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## ABSTRACT

**Introduction:** Sepsis is a well-recognised medical emergency requiring aggressive medical management, often in a critical care setting. Granulomatosis with Polyangiitis (GPA) (previously named Wegener's Granulomatosis) is a type of primary systemic antineutrophil cytoplasmic antibodies (ANCA) associated vasculitis (AAV) [2-4]. AAV can present with a variety of symptoms including those which mimic infective disease. Differentiation between these two diseases is extremely important because their respective treatments differ significantly and delays in commencing therapy can be fatal.
**Case Presentation:** A 70 year old Caucasian gentleman presented with symptoms suggestive of severe sepsis who failed to respond to standard treatment. However an autoimmune screen revealed that he was in fact suffering from severe generalised GPA. Despite aggressive treatment

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his disease progressed rapidly and he passed away on day 20 of his admission.
**Conclusion**: This case report describes a rare and potentially fatal disease which can present with a variety of non specific symptoms. It highlights the importance of differentiating between AAV and syndromes that may mimic AAV, particularly infection (including meningitis) in the ICU settings.

*Keywords: Sepsis; granulomatosis with polyangiitis; antineutrophil cytoplasmic antibodies; ANCA-associated vasculitis.*

## 1. INTRODUCTION

Sepsis is a well-recognised medical emergency requiring aggressive medical management, often in a critical care setting. Without treatment mortality rates are high but are dramatically lowered with early intervention [1]. Granulomatosis with Polyangiitis (GPA) (previously named Wegener's Granulomatosis) is a type of primary systemic antineutrophil cytoplasmic antibodies (ANCA) associated vasculitis (AAV) [2-4]. It is the most common type amongst this group of diseases, usually affecting the kidneys, lungs, ears, nose and sinuses, involving small and medium sized blood vessels. GPA occurs in about 1/25,000 people. It is most common among caucasians but can occur in all ethnic groups. It usually affects middle aged and elderly people but can affect young adults and children. It usually begins as localised granulomatous inflammation of the upper and lower airways but can progress to a severe generalised systemic vasculitis [2-4]. This case describes an elderly gentleman presenting with symptoms suggestive of sepsis with possible meningeal involvement. However he was in fact suffering from severe GPA.

## 2. PRESENTATION OF CASE

A 70 year old gentleman presented to hospital following a fall. He lived alone and was fully independent with no cognitive impairment. His past medical history consisted of congestive heart failure and chronic obstructive pulmonary disease (COPD). Two months previously he had been admitted for an infective exacerbation of COPD. On this subsequent admission he presented with history of recent increased shortness of breath as well as nonspecific constitutional complaints such fevers, fatigue, earache and loss of appetite for the several last weeks without evidence of specific organ involvement. He had bilateral coarse crackles on auscultation of his chest, no focal neurology and a Glasgow Coma Scale (GCS) of 15. Initial blood tests revealed a raised white cell count, C-reactive protein (CRP) and an acute kidney injury. He was diagnosed with a second infective exacerbation of COPD and was admitted.

On day two of his admission he became increasingly confused. His GCS was now 9 and he developed red, non-blanching petechiae, areas of palpable purpura and skin ulcers on his feet and lower legs. Despite the patient was under sedation, the left lower quadrant abdomen was tender on examination (compatible with the presence of splanchnic vasculitis) and also presented with sinus tenderness, conjunctivitis, rhinitis and epistaxis. He condition deteriorated rapidly requiring intubation and ventilation on the Critical Care Unit. An initial diagnosis of septic shock with possible meningitis was made. Intravenous antimicrobials and dexamethosone were commenced as per hospital guidelines.

Serial blood tests revealed a rapid progression to multi-organ failure. Full blood counts revealed normochromic normocytic anaemia, and leucocytosis with neutropil predominance. Inflammatory markers (CRP and erythrocyte sedimentation rate (ESR)) remained high, also the rheumatoid factor was positive. His renal function deteriorated requiring haemofiltration. Liver function tests were significantly deranged. Serum albumin and total protein were decreased. A significant coagulopathy was also present. Urine cultures were performed, urine analysis showed a patron of crescentic necrotizing glomerulonephritis characterized by urinary sediment with erythrocyte casts indicating glomerular involvement. Proteinuria also was detected. Samples were sent to exclude the presence of infections that can produce granulomas (eg, tuberculosis), vasculitis, or necrosis, including those for antinuclear antibodies, anti-glomerular basement membrane (anti-GBM) antibodies, C3 and C4, cryoglobulins, hepatitis serologies, HIV, as well as liver function tests, tuberculosis screen, and blood cultures including mycobacterial and fungal infections and other atypical infections. Microbiological studies of bronchoalveolar lavage were negatives. A cerebrospinal fluid culture was performed but was delayed until the coagulopathy had been

corrected. An autoimmune screen was also performed. Chest X-rays revealed bilateral patchy opacities and bilateral pleural effusions.

Despite aggressive antibiotic and fluid resuscitation he showed little improvement. Placement of a nasogastric tube provoked excessive bleeding from his nostril and frank blood had to be suctioned intermittently from his endotracheal tube. The presence of circumferential subglottic red friable tissue had been noted at intubation. A bedside bronchoscopy was performed which showed a profuse alveolar haemorhage but due to his respiratory instability formal lung biopsies were not performed. Chest computed tomography (CT) showed bilateral haemorrhages, small pulmonary nodules and bilateral pleural effusions [Fig. 1]. There was no evidence of a cavitating lesion but a large splenic infarct was noted [Fig. 2]. A CT head scan was normal. Magnetic resonance (MRI) imaging was recommended but the patient had become too unstable for transfer.

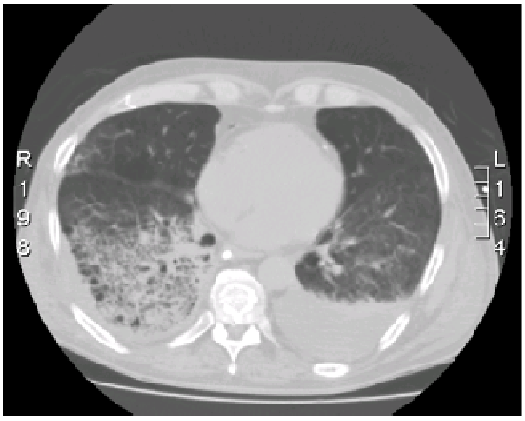


**Fig. 1. CT Chest image revealing, pulmonary nodules, haemorrhages and pleural effusions**

His skin lesions spread and evolved from petechiae to palpable purpura, ecchymoses and blistering predominantly affecting his neck and shoulders. Skin biopsies were taken but results returned as non-specific inflammation: Necrotizing granulomatous inflammation, non-specific ulceration and superficial dermal and epidermal necrosis without inflammation. Lumbar puncture, blood, urine, sputum and bronchial lavage cultures were all negative. Sepsis was now much less likely. However, after the autoimmune screen returned positive for ANCA-C and anti-Proteinase-3- antibodies (anti-PR3 antibodies). A new diagnosis of severe systemic GPA was made.

Methylprednisolone and cyclophosphamide therapy was rapidly commenced but our patient continued to deteriorate requiring increasingly invasive support. The possibility of a plasma exchange was discussed but his illness had progressed too far for this to be of benefit. Following discussion with his family, treatment was eventually withdrawn and our patient passed away on day 20.

## 3. DISCUSSION

GPA is an autoimmune disease of unknown origin, consisting of granulomatous inflammation and necrotizing vasculitis affecting small to medium sized blood vessels. The European Vasculitis Study group classifies the disease as either localised, early systemic or generalised [5]. Localised disease refers to cases involving only the upper and lower respiratory tract. Patients most frequently present with chronic destructive sino-nasal lesions but can also present with severe alveolar haemorrhage which can be fatal [6]. Early systemic disease refers to involvement of additional organ systems without renal involvement and without evidence of end organ failure. Generalised disease means patients have evidence of glomerulonephritis or other end organ failure. Central nervous system and meningeal involvement are rare but recognised features in some patients [3,4]. Our patient showed evidence of multiple end organ involvement and thus we believe he was suffering from severe generalised GPA.

It can present in different ways in different people, depending on the severity and the organs involved. This can make diagnosis very difficult. It is not uncommon for patients to have had mild symptoms for months or even years before seeing a doctor at all. As seen in this case routine blood tests, chest X-rays and chest CT scans [Fig. 1] are commonly non-specific, showing evidence of inflammation or possible infection. Histology of lesions can be granulomatous, necrotic or vasculitic in nature and IgG- and/or IgA-containing immune deposits may be found in blood vessel walls [4,5]. Skin biopsies for our patient came back as non-specific inflammation, while no cutaneous lesion is specific for GPA, several histopathologic entities, including necrotizing granulomatous inflammation are characteristic (our case). A biopsy of an affected organ (kidney and lung) was not feasible due to his clinical instability (profuse bleeding and $FiO_2$ requirements). However as high dose corticosteroids therapy

was well established at the time of biopsy the lesions could still due to GPA. His reduced cognitive status could also be the result of cranial involvement of this disease. A CT head appeared normal which is commonly the case in central nervous system disease. Lesions are normally only detected on a MRI scan. However as mentioned above MRI was not performed because the patient was too unstable [3,4]. He did however have some positive findings to support a diagnosis of GPA. The autoimmune screen returned positive for cANCA which is strongly associated with the disease and with the severity of the initial immune response [7,8]. Combining immunofluorescence and ELISA techniques (it was our case) enhances the sensitivity and specificity of a diagnosis of an ANCA-associated vasculitis (AAV) to 96% and 98.5%, respectively. Also tests returned positive for anti-PR3 antibodies which are highly specific (>90%) for GPA [9]. The CT abdomen revealed evidence of splenic infarction [Fig. 2] which is a well-recognised complication of GPA [10].

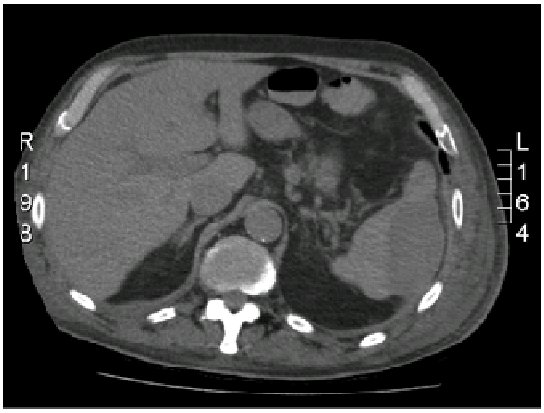


**Fig. 2. CT Abdomen revealing a large low attenuation area in the lateral aspect of the spleen consistent with infarction**

In some settings, a biopsy of an affected organ is not feasible or should be delayed. In such patients, a presumptive diagnosis of AAV can be made if there is a high probability of AAV based upon clinical findings (such as new-onset rhinosinusitis, pulmonary nodules, or alveolar hemorrhage), a positive test for ANCA, and a low likelihood of another etiology.

The initiation of therapy without a confirmatory biopsy may be necessary, such as in the severely ill ventilator-dependent patient without extrapulmonary involvement in whom the performance of a lung biopsy to obtain adequate tissue may result in significant morbidity or mortality (our case). We commenced intravenous Methylprednisolone and nasogastric cyclophosphamide. Immunosuppression with high dose corticosteroids and disease modifying agents like these is the mainstay of treatment [2-4]. Early initiation of therapy is essential and can significantly improve prognosis. However this can be complicated as such treatments carry a significant risk of developing severe catastrophic infections as well as other side effects which must be considered carefully before prescribing them for critically ill patients [11]. The use of plasma exchange in GPA is still under investigation. It is an expensive and nonselective therapy with significant risks. However it is thought to have potential for treating severe, generalised cANCA positive vasculitis [12]. As mentioned above, this intervention was considered for our patient however his disease had progressed too far by this stage.

## 4. CONCLUSIONS

This case report highlights the importance of considering systemic vasculitis as a differential diagnosis in any patient with multi-system disease. It is important to differentiate between AAV and syndromes that may mimic AAV, including other vasculitic disorders that affect small- and medium-sized vessels e infections, especially those due to slow-growing fungi or acid-fast organisms.

The rapid disease progression in this case limited our ability to perform certain definitive tests, hindering a definitive final diagnosis. However with the evidence presented above there was a high degree of suspicion for a diagnosis of severe systemic GPA rather than sepsis. Early intervention is essential and one should strongly consider including an autoimmune screen as an initial investigation for such patients.

## CONSENT

As our patient passed away from this illness we have full written consent to write and publish this case report from his next of kin.

## ETHICAL APPROVAL

It is not applicable.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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