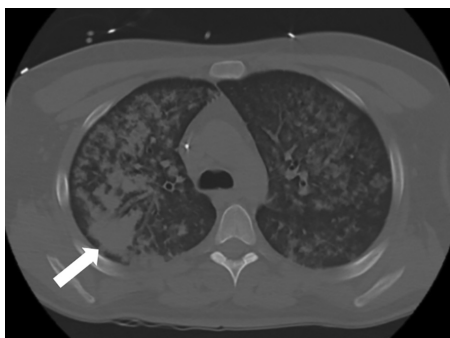


Seronegative granulomatosis with polyangiitis in multiple organ dysfunction

Introduction

This article presents a case of a 28-year-old previously healthy man found unresponsive in a pool of blood. Computed tomography demonstrated mucosal thickening in the sinus cavities of head and severe diffuse alveolar haemorrhage on the entire lung field. Further investigation showed acute heart, liver, and kidney failure, and leukocytoclastic angiitis in his back, arms and legs. The patient had an excellent therapeutic response with resolution of diffuse alveolar haemorrhage.

Figure 1. Non-contrast computed tomography of the chest demonstrating bilateral ground glass opacities and a right lobe consolidation (white arrow) consistent with diffuse alveolar haemorrhage.



Mr Hunter Spitz, Medical Student, Department of Medicine, Wright State University Boonshoft School of Medicine, Dayton, Ohio, United States

Dr Stella Pak, Physician, Department of Medicine, Kettering Medical Center, Kettering, Ohio, United States

Dr Damian Valencia, Physician, Department of Medicine, Kettering Medical Center, Kettering, Ohio, United States

Mr Andrew Kilgore, Medical Student, Department of Medicine, Wright State University Boonshoft School of Medicine, Dayton, Ohio, United States

Dr Adam Fershko, Physician, Department of Medicine, Kettering Medical Center, Kettering, Ohio, United States

Correspondence to: Dr S Pak (stella.pak@ketteringhealth.org)

This case is reported to increase physician awareness of seronegative granulomatosis with polyangiitis. Multiple organ system involvement of seronegative granulomatosis with polyangiitis demonstrated in this case is very rare. This case highlights that the diagnosis of granulomatosis with polyangiitis

should be established based on clinical assessment rather than ANCA positivity.

Discussion

Granulomatosis with polyangiitis is a necrotizing granulomatous vasculitis, wherein autoantibodies, known as anti-

CASE REPORT

An otherwise healthy 28-year-old man was found unresponsive in a pool of blood in his bathtub. His medical history was significant for intermittent episodes of haematemesis with frothy pink sputum over the previous month. On presentation, his blood pressure was 71/46 mmHg, heart rate was 145/min, body temperature was 36.5°C, respiratory rate was 30/min and oxygen saturation was 54% on room air. On examination, the patient was tachypnoeic with laboured breathing and agonal gasps, diminished breath sounds bilaterally in all lung fields, dry mucous membranes, sunken eyes, decreased skin turgor, cervicothoracic scoliosis, and erythematous pinpoint lesions involving the back and bilateral upper and lower extremities.

Laboratory studies revealed C-reactive protein <2.90 mg/litre, erythrocyte sedimentation rate 13 mm/hr, white blood cell count 15 500/ul, and haemoglobin 11.6 g/dl, creatinine 1.71 mg/dl, aspartate transaminase 170 IU/litre and alanine transaminase 107 IU/litre. Urinalysis was notable for epithelial casts, microscopic haematuria and mild proteinuria. Transthoracic echocardiography on admission showed severe diffuse hypokinesis of the left ventricle with ejection fraction of 20–25% and grade 2 diastolic dysfunction. P-ANCA, C-ANCA, antinuclear antibody, rheumatoid factor, anti-Scl-70 antibody, anti-RNP antibody, Sjögren syndrome A and B antibodies, and anti-Smith antibody were all negative. Arterial blood gas revealed pH 7.14, pCO₂ 70 mmHg, and pO₂ 45 mmHg at oxygen saturation of 62.6%. The patient was emergently intubated and placed on mechanical ventilation.

Computed tomography of the chest revealed bilateral ground glass opacities and right lobe consolidation (Figure 1). Oesophagogastroduodenoscopy and

bronchoscopy findings were non-contributory, although bronchoalveolar lavage did reveal numerous pigmented macrophages. A skin biopsy performed to evaluate the rash on his back showed leukocytic infiltration into the vasculature walls, but without complement or immunoglobulin deposition on direct immunofluorescence staining.

Considering the patient's history of chronic sinusitis and acute haemoptysis from massive diffuse alveolar haemorrhage, treatment with five cycles of plasmapheresis and methylprednisolone therapy was started for suspected granulomatosis with polyangiitis. The patient had an excellent response to the 7-day treatment course with subsequent extubation, resolution of acute renal and hepatic injury, and improved ejection fraction on transthoracic echocardiography (45–50%) measured on the 12th day of hospitalization. The patient was discharged on prednisone 80 mg daily. Approximately 2 months after discharge, repeat transthoracic echocardiography showed normal systolic and diastolic function of the left ventricle with ejection fraction of 55–60%.

The patient was started on cyclophosphamide infusions (1200 mg) every 2 weeks for three doses, then gradually tapered over the following 3 months. Prednisone was also tapered from 80 mg to 20 mg daily during this period. The patient was then started on azathioprine 200 mg daily and prophylactic antibiotic coverage with sulfamethoxazole-trimethoprim 800 mg-160 mg three times a weekly. At the patient's 2-year follow-up visit, he reported still experiencing chronic sinusitis, diffuse arthromyalgia, and profound fatigue with little improvement of the skin rash. However, there was no recurrence of diffuse alveolar haemorrhage or dysfunction in the cardiac, hepatic or renal system.

neutrophil cytoplasmic antibodies, are directed against neutrophil granule proteins and induce a systemic inflammatory response (Jennette et al, 2013; Weiner and Segelmark, 2016). These antibodies can be useful as a diagnostic aid, although their absence cannot rule out granulomatosis with polyangiitis (Moreno-González et al, 2014). In the absence of serum autoantibodies, but with high clinical suspicion, the diagnosis of granulomatosis with polyangiitis can be made if two or more of the following are present: oral ulcers or purulent or bloody nasal discharge, presence of nodules, fixed infiltrates or cavities on chest X-ray, microhaematuria or red cell casts, granulomatous inflammation within an arterial wall or a perivascular or extravascular area (Leavitt et al, 1990).

The most commonly affected organ in patients with granulomatosis with polyangiitis is the lung, which occurs in 90% of cases. Diffuse alveolar haemorrhage, a potentially fatal complication present in 5% of patients with granulomatosis with polyangiitis, is defined by the clinical triad of haemoptysis, mild anaemia and progressive hypoxaemia (Vaishnav et al, 2012; Vanoli et al, 2017). Multiorgan involvement in seronegative granulomatosis with polyangiitis is rare and only four other cases of acute heart failure have been reported (Kim et al, 2013; Kyaw et al, 2017).

The treatment goal of diffuse alveolar haemorrhage secondary to granulomatosis with polyangiitis is to achieve remission using immunosuppressive therapy. With the aforementioned therapeutic regimen more than 75% of patients achieve sustained remission of disease (Mukhtyar et al, 2009; Lara and Schwarz, 2010).

Conclusions

This case has detailed an atypical case of seronegative granulomatosis with polyangiitis involving multiple organs. While uncommon, clinicians are urged to maintain a high level of suspicion for seronegative granulomatosis with polyangiitis if physical examination and medical history are fitting. Early identification and therapeutic intervention will drastically reduce morbidity and mortality in these patients. **BJHM**

Jennette JC, Falk RJ, Bacon PA et al. 2012 revised international chapel hill consensus conference nomenclature of vasculitides. *Arthritis Rheum.* 2013 Jan;65(1):1–11. <https://doi.org/10.1002/art.37715>

Kim SH, Park J, Bae JH, Cho MS, Park KD, Jeong JH. ANCA-negative Wegeners granulomatosis with multiple lower cranial nerve palsies. *J Korean Med Sci.* 2013;28(11):1690–1696. <https://doi.org/10.3346/jkms.2013.28.11.1690>

Kyaw H, Misra D, Mani MM, Park WJ, Shinnar M. Unusual cardiac involvement in granulomatosis with polyangiitis manifesting as acute congestive heart failure. *Anatol J Cardiol.* 2017 Aug;18(2):158–160. <https://doi.org/10.14744/AnatolJCardiol.2017.7732>

Lara AR, Schwarz MI. Diffuse alveolar hemorrhage. *Chest.* 2010 May;137(5):1164–1171. <https://doi.org/10.1378/chest.08-2084>

Leavitt RY, Fauci AS, Bloch DA et al. The American College of Rheumatology 1990 criteria for the classification of Wegeners granulomatosis. *Arthritis Rheum.* 1990 Aug;33(8):1101–1107. <https://doi.org/10.1002/art.1780330807>

Moreno-González G, Corral-Ansa L, Sabater-Riera J, Solanich-Moreno X, Mañez-Mendiluce R. Pulmonary thromboembolism and diffuse alveolar hemorrhage in granulomatosis with polyangiitis vasculitis. *Respir Care.* 2014 Dec 01;59(12):e206–e209. <https://doi.org/10.4187/respcare.03162>

Mukhtyar C, Guillevin L, Cid MC et al; European Vasculitis Study Group. EULAR recommendations for the management of primary small and medium vessel vasculitis. *Ann Rheum Dis.* 2009 Mar 01;68(3):310–317. <https://doi.org/10.1136/ard.2008.088096>

Vaishnav KU, Bhatt C, Desai A. 2012. Diffuse alveolar haemorrhage in granulomatosis with polyangitis (Wegener's) with coexistent

LEARNING POINTS

- Diagnosis of granulomatosis with polyangiitis should be made based on clinical presentation and medical history, rather than ANCA positivity.
- The clinical diagnosis of granulomatosis with polyangiitis can be made if two or more of oral ulcers or purulent or bloody nasal discharge, presence of nodules, fixed infiltrates or cavities on chest X-ray, microhaematuria or red cell casts, granulomatous inflammation within an arterial wall or a perivascular or extravascular area.
- Plasmapheresis is indicated in patients with granulomatosis with polyangiitis who have severe lung involvement and alveolar haemorrhage or severe renal disease with creatinine >5.8 mg/dl.
- Diffuse alveolar haemorrhage is the most severe complication of small vessel vasculitis and is thought to occur in 5% of patients with granulomatosis with polyangiitis.
- Seronegative granulomatosis with polyangiitis can present with multisystemic manifestations, including acute heart failure.

rheumatoid arthritis. *BMJ Case Rep.* 2012 Aug 8;2012. pii: bcr2012006184. <https://doi.org/10.1136/bcr.2012.006184>

Vanoli J, Riva M, Vergano B, D'Andrea G, Imperio V, Pozzi MR, Grassi G. Granulomatosis with polyangiitis presenting with diffuse alveolar hemorrhage requiring extracorporeal membrane oxygenation with rapid multiorgan relapse. *Medicine.* 2017 Mar;96(13):e6024. <https://doi.org/10.1097/MD.0000000000006024>

Weiner M, Segelmark M. The clinical presentation and therapy of diseases related to anti-neutrophil cytoplasmic antibodies (ANCA). *Autoimmun Rev.* 2016 Oct;15(10):978–982. <https://doi.org/10.1016/j.autrev.2016.07.016>

Forthcoming case reports

- Apixaban for stroke prevention in a patient with a mechanical heart valve
- Warfarin-resistant left ventricular thrombus completely dissolved by rivaroxaban
- Gastrointestinal bleeding in a patient on multiple medications including edoxaban
- A swollen leg and cerebral infarctions in a 49-year-old woman
- Focal limb weakness (monoparesis): when family history holds the key to diagnosis
- Heidenhain variant of Creutzfeldt-Jakob disease

Case Report

A feverish ju with a diagn

Case Report

Acute interstitial nephritis caused by two different proton pump inhibitors

Introduction

Acute interstitial nephritis is an important cause of acute kidney injury and drug-induced acute kidney injury. It is characterized by a triad of fever, rash, and eosinophilia. The pathogenesis is thought to be immune-mediated. The diagnosis is often made by renal biopsy. The treatment is usually with corticosteroids. The prognosis is generally good, but some patients may have persistent kidney damage.

Discussion

This case report describes a patient with acute interstitial nephritis who presented with fever, rash, and eosinophilia. The patient was treated with corticosteroids and recovered. This case highlights the importance of considering acute interstitial nephritis in the differential diagnosis of acute kidney injury in patients with fever, rash, and eosinophilia. The diagnosis is often made by renal biopsy. The treatment is usually with corticosteroids. The prognosis is generally good, but some patients may have persistent kidney damage.

Conclusion

This case highlights the importance of considering acute interstitial nephritis in the differential diagnosis of acute kidney injury in patients with fever, rash, and eosinophilia. The diagnosis is often made by renal biopsy. The treatment is usually with corticosteroids. The prognosis is generally good, but some patients may have persistent kidney damage.