CASE REPORT

Rare cause of respiratory failure in a young woman: isolated diffuse alveolar haemorrhage requiring extracorporeal membrane oxygenation

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SUMMARY

A previously healthy 21-year-old young woman presented with worsening dyspnoea and haemoptysis. Imaging was suggestive of widespread pulmonary haemorrhage. There was no other organ system involvement in particular no evidence of renal involvement. Raised antimyeloperoxidase titres allowed diagnosis of isolated diffuse alveolar haemorrhage (DAH) secondary to microscopic polyangiitis (MPA). The patient rapidly deteriorated with worsening respiratory failure despite invasive mechanical ventilation and required extracorporeal membrane oxygenation (ECMO). This maintained the patient long enough to allow aggressive therapy in the form of immunosuppression and plasma exchange. She made a remarkable recovery and is asymptomatic 2 years on. Isolated DAH in the absence of renal disease is an atypical presentation of MPA and can lead to diagnostic uncertainty. A literature review reveals increasing reports of successful use of ECMO in severe DAH due to pulmonary vasculitis. Despite this, the need for systemic anticoagulation in the presence of pre-existing haemorrhage remains a challenging dilemma.

BACKGROUND

Microscopic polyangiitis (MPA) is a rare vasculitis associated with antimyeloperoxidase (MPO) antibodies. It most commonly presents with multiple

organ involvement, particularly kidney and lung, with diffuse alveolar haemorrhage (DAH) being the most dreaded acute pulmonary manifestation. DAH is often rapidly fatal if the underlying cause cannot be promptly identified and treated.

Here, we present a case of a young woman, admitted on a Friday evening with catastrophic DAH due to underlying MPA who ultimately required extracorporeal membrane oxygenation (ECMO). This case highlights the diagnostic uncertainties in single-organ involvement of MPA. This is particularly so in district general hospitals with limited access to rapid out-of-hours anti-neutrophil cytoplasmic antibody (ANCA) testing. This case also emphasises the increasing role of ECMO in patients with DAH due to MPA, for whom it may be life saving.

CASE PRESENTATION

A previously fit and well 21-year-old young woman was admitted on a Friday evening to a district general hospital. She presented with 2 weeks of worsening dyspnoea and increasing haemoptysis which was associated with nocturnal sweats and 3 months of lethargy. She denied any other symptoms including rash, nasal/sinus involvement, abdominal pain or haematuria. One week prior, she had seen her general practitioner (GP) and was at that time diagnosed with a viral chest infection.

On admission the patient was hypotensive with a blood pressure of 92/50 mm Hg and tachycardic with a pulse rate of 112 bpm. There was evidence of significant respiratory distress with increased respiratory rate of 28 per min and low oxygen saturations on air (88%–90%). Temperature was 37.6°C. Chest auscultation was notable for bilateral crepitations and reduced air entry at both bases. Abdomen was soft, non-tender and neurological examination was unremarkable. There was no rash on inspection.

The patient's medical history included infective meningitis at age 4 and occasional migraine. She was not taking any regular medication. Occupation was office based with no environmental exposures and no recent travel abroad. No significant family history was elicited.

INVESTIGATIONS

Bedside urine dipstick was unremarkable, in particular being negative for blood and protein.

Figure 1 Chest X-ray on admission showing diffuse bilateral alveolar consolidation.

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Figure 2 CT chest with contrast on admission.

Haematology results revealed a haemoglobin of 74 g/L and mean corpuscular volume (MCV) of 92.3 fL. Total white cell count was $9.7 \times 10^9/\text{L}$ with a neutrophilia of $9.01 \times 10^9/\text{L}$ and eosinophils of $0.00 \times 10^9/\text{L}$.

Biochemistry results showed normal renal function with a creatinine of 70 $\mu\text{mol/L}$ and urea of 4.2 mmol/L. C-reactive protein was raised at 137 mg/L.

Arterial blood gas on admission was consistent with a type I respiratory failure. Results included a pH of 7.506, partial pressure carbon dioxide (pCO_2) 4.17 kilopascal (kPa), partial pressure oxygen (PO_2) 7.89 kPa, bicarbonate 24.2 mmol/L and base

Figure 3 Chest X-ray on day 2 while in intensive therapy unit showing progressive diffuse alveolar haemorrhage.

Figure 4 Chest X-ray 1 month post-treatment with methylprednisolone, rituximab, plasma exchange therapy and extracorporeal membrane oxygenation showing complete resolution of alveolar haemorrhage.

excess of 1.3 mmol/L while receiving inhaled oxygen via 35% venturi mask.

Chest X-ray on admission demonstrated diffuse bilateral alveolar consolidation ([figure 1](#)). The patient went onto have a CT chest with contrast which revealed extensive bilateral consolidation with ground-glass attenuation in a central distribution ([figure 2](#)).

Bronchoscopy plus lavage while on the intensive therapy unit (ITU) demonstrated inflamed mucosa with frank haemorrhage.

Immunology results returned on day 2 with a raised anti-MPO level of 196 (IU/mL) with negative antglomerular basement membrane antibodies and negative antiproteinase 3 antibodies.

DIFFERENTIAL DIAGNOSIS

Diffuse alveolar haemorrhage was suspected on the basis of initial imaging and investigations with vasculitis as a likely cause. However, a severe infective interstitial pneumonia was not ruled out.

Once the raised anti-MPO titre was revealed, the diagnosis of diffuse alveolar haemorrhage secondary to microscopic polyangiitis was made.

TREATMENT

Shortly after admission, the patient started treatment with broad spectrum antibiotics and oseltamivir to cover for infective pneumonia. Her oxygen demand increased over the course of the first 4 hours by which time she was requiring a fraction of inspired oxygen (FiO_2) of 60% via venturi mask. In view of this and her haemodynamic instability, intensive care support was sought early and she was promptly transferred to ITU.

During her first day in ITU, she became increasingly haemodynamically unstable and remained hypotensive with arterial line blood pressures of 81 mm Hg systolic, 48 mm Hg diastolic and mean arterial pressure 61 mm Hg. She was also persistently tachycardic with heart rate between 100 and 120 bpm. Blood

products including packed red cells, platelets and clotting factors were infused alongside intravenous hydrocortisone and tranexamic acid. She required inotropic support in the form of a norepinephrine solution infusion of 4 mg per 50 mL at a rate of 6 mL/hour. She remained persistently hypoxic and began showing evidence of respiratory fatigue so the decision was made to proceed to intubation and invasive ventilation.

By day 2, she was being ventilated via a size eight endotracheal tube and bilevel positive airway pressure. Ventilator settings included an inspiratory pressure of 30 cm of water (cm H₂O), positive end-expiratory pressure of 12 cm H₂O, FiO₂ 100%, respiratory rate 12 breaths per min and inspiratory time of 2 s on assisted spontaneous breathing. Unfortunately, she continued to deteriorate despite adjustment of the ventilator settings and a trial of high-frequency oscillatory ventilation with oxygen saturations 80%–85% and arterial pO₂ of 7.53 kPa and pCO₂ of 5.68 kPa. There was significant ongoing alveolar bleeding, and despite regular suctioning she intermittently desaturated to oxygen saturations as low as 76%. Repeat chest X-ray revealed progressive bilateral widespread DAH (figure 3). As such, veno-venous ECMO support was requested from the closest ECMO centre who unfortunately had no capacity within their unit to accept another patient. The second closest ECMO centre was three counties away, however, did have capacity and promptly sent a team to retrieve the patient and initiate ECMO in situ.

Prior to ECMO initiation, she had two large bore cannulas inserted via left and right common femoral vein percutaneous approach under fluoroscopic guidance. Imaging confirmed cannula tip positions at the inferior vena cava for drainage and at the entrance to the right atrium for blood return. ECMO was started alongside a heparin infusion with an initial target activated clotting time (ACT) of 180 s. Shortly after this was started, the anti-MPO titre returned and the initial diagnosis of ANCA-associated vasculitis was made.

On arrival at the ECMO centre hospital, she began pulsed intravenously methylprednisolone and rituximab 375 mg/m² as per the rituximab versus cyclophosphamide for ANCA-associated vasculitis protocol.¹ In addition to this, she underwent 1 week of plasma exchange therapy. Prophylactic cotrimoxazole was also started.

OUTCOME AND FOLLOW-UP

In this case, initial anticoagulation with a target ACT of 180 s did not appear to significantly aggravate her pre-existing pulmonary haemorrhage nor lead to extrapulmonary bleeding. Rapid remission of alveolar haemorrhage was successfully induced with rituximab and methylprednisolone (three doses of 1 g). In total, the patient received 6 days of ECMO after which she went on to make a remarkable recovery. Repeat chest X-ray at 1 month post-therapy demonstrated complete resolution of alveolar haemorrhage (figure 4). Remission was maintained with a reducing dose of prednisolone (currently down to 4 mg) and 6-monthly rituximab infusions which were stopped after 2 years. She continues to be asymptomatic 3 years since the initial presentation with an anti-MPO titre of 1.9 IU/mL.

DISCUSSION

It is uncommon for MPA to present with isolated DAH. In particular, it is unusual for such severe lung disease to occur in the absence of any detectable renal involvement. A large study² of 697 patients with MPA found renal involvement in 86.9% of patients while pulmonary haemorrhage only occurred in 11.3%.

The apparent single-organ involvement, in particular lack of detectable renal disease, led to a degree of diagnostic uncertainty in this case. This was compounded by a lack of rapid out-of-hours ANCA testing available at that time. By the time ANCA results were available, the patient had suffered fulminant respiratory failure despite optimal invasive ventilation. It is reasonable to consider that without early consideration of ECMO, this young woman would have likely not survived. One aspect this case highlights is that ANCA-associated vasculitis (such as MPA) must always be considered in DAH even when this appears to occur in isolation. Failure to do so at an early stage can lead to missing a narrow window of opportunity for early intervention.

There are limited numbers of case reports regarding ECMO use in DAH secondary to pulmonary vasculitis due to the low incidence of this presentation.² However, there does appear to be an increasing role for veno-venous ECMO as a rescue therapy in severe DAH secondary to pulmonary vasculitis.^{3–5} Its use is complicated by the need for concurrent systemic anticoagulation to reduce the risk of thrombus within the ECMO circuit. The potential to aggravate ongoing bleeding is of significant concern. Nevertheless, current ECMO guidelines⁶ recommend that there are no absolute contraindications to its use and advocate a case by case assessment. Current recommendations for ECMO⁶ are to use heparin infusions with a target ACT of 180–200 s. It is also recommended⁶ to reduce the target ACT to 180 s should bleeding occur and to discontinue the heparin if bleeding persists despite this. However, there is little guidance on managing anticoagulation in patients who are already bleeding prior to ECMO initiation.

A review of published case reports reveals different approaches to anticoagulation. One case report³ of DAH secondary to granulomatosis with polyangiitis (GPA) describes successful ECMO use alongside a heparin infusion with a target ACT of 140–160. In this case, there was no worsening of alveolar haemorrhage or reported clot formation within the ECMO circuit. After 3 weeks, the patient was weaned off ECMO and survived to discharge.

In contrast, another case report⁴ demonstrates use of ECMO with no initial systemic anticoagulation. The authors describe two patients with DAH due to systemic lupus erythematosus who required ECMO support. Of the two patients, one died from multiorgan failure due to ongoing bleeding and septic shock. The other patient developed clots within the ECMO circuit and so required temporary heparin infusion which was soon stopped. This did not cause any secondary bleeding and the patient survived to discharge.

A third case study⁵ regarding a patient with DAH due to GPA used a delayed approach to anticoagulation. While an initial heparin bolus of 2500 IU was given after cannulation, systemic heparin infusion was delayed for 48 hours. However, there was again formation of clots within the ECMO circuit on day 2 and so a heparin infusion was commenced with target activated partial thrombin time ratio between 1.5 and 1.8 (no target ACT range given). There was no further clot formation or worsening of bleeding on starting the heparin infusion. The patient required 20 days of ECMO after which he was weaned off and survived to discharge.

Despite the lack of clear guidance for ECMO in patients with DAH due to underlying pulmonary vasculitis, there appears to be a growing indication for its use. However, it is difficult to ascertain fully what role ECMO can play in DAH due to pulmonary vasculitis from case reports alone. While these cases do occur, they are not always reported on. It is also probable that examples where the patient survives to discharge are more likely to be published which may well lead to bias

Patient's perspective

- ▶ My first symptoms began around 2-3 months prior to my admission hospital. I was feeling lethargic but shrugged this off as symptoms following a viral infection after a trip to the doctors. A week prior to my stay in hospital I brought up clots of blood several times.
- ▶ The night prior to my admittance I became very short of breath and faint, I then began coughing up larger amounts of blood and suffered with hot/cold sweats throughout the night. The following day I was very weak so was referred to the hospital after an out of hours GP advised that my resting pulse was higher than usual, at this point I was not particularly concerned for my well-being and was sure that I would be discharged the same day, but as the day went on my lung function deteriorated and I was moved to the ITU.
- ▶ I was still optimistic about my health even then; I considered myself fit/healthy and was eager to keep the atmosphere calm and positive for my family. The rest of my time in my admitting hospital is very vague as the last thing I remember is waking up there the following morning and then waking up in the ECMO centre. At this point I was fearful as I was unsure of where I was/what had happened to me. This soon receded as I was made aware of the situation and my current state of health.
- ▶ During my time in the ECMO ward and ITU I struggled with anxiety and panic attacks following the sedation as I was left disorientated and confused at times, so struggled to string together the events of the previous week. I struggled to tell the difference between reality and imagination which left my mental state somewhat delicate for a few days following.
- ▶ My diagnosis affected me for the first 6–12 months following my recovery as I was more careful with my energy levels and what I was eating. However, 3 years on I would consider myself equally as fit/healthy as I was prior to my admission. I exercise regularly and have tapered prednisolone down to 4 mg daily. I do suffer from anxiety from time to time when I become short of breath as this triggers flashbacks to my time in hospital. Thinking back to my time in hospital I was never concerned for my life, I felt completely secure and trusted the medical professionals who surrounded me during my diagnosis and recovery, they acted fast and was able to provide me with the best care to keep me stable and allow me to move on from the circumstances with barely any change to my day to day life.

favouring the use of ECMO. This leaves scope for further studies into the effectiveness of ECMO including the impact of systemic anticoagulation in DAH. In our patient, this proved to be a life-saving bridge therapy while her underlying MPA could be suppressed.

Learning points

- ▶ Single-organ involvement is an uncommon but acknowledged manifestation of microscopic polyangiitis.
- ▶ High levels of suspicion for ANCA-associated vasculitis (such as microscopic polyangiitis (MPA)) with isolated DAH allows for earlier ANCA confirmation and aggressive immunosuppression.
- ▶ Diffuse alveolar haemorrhage (DAH) due to MPA can be rapidly fatal and requires a multidisciplinary approach including early involvement of intensive therapy unit and consideration of transfer to tertiary centres if required.
- ▶ Despite the risks of anticoagulation with extracorporeal membrane oxygenation in DAH, there are increasing reports of its successful application, in which cases it may be life saving.

The majority of published case reports describing ECMO use in pulmonary vasculitis are written from the perspective of a tertiary ECMO centre. In these cases, access to ECMO can be rapid and often the diagnosis is already made prior to the patient arriving. Our case report highlights some of the challenges facing a small, district general hospital where rapid ECMO access is not possible and indeed can require travelling across many county borders.

A multidisciplinary approach to management including early ITU involvement is crucial. This allows early referral for ECMO to be considered on a case by case basis if conventional ventilation fails. Finally, vasculitides such as MPA must be considered even when DAH occurs in isolation.

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REFERENCES

- 1 Stone JH, Merkel PA, Spiera R, *et al.* Rituximab versus cyclophosphamide for ANCA-associated vasculitis. *N Engl J Med* 2010;363:221–32.
- 2 Sugiyama K, Sada KE, Kurosawa M, *et al.* Current status of the treatment of microscopic polyangiitis and granulomatosis with polyangiitis in Japan. *Clin Exp Nephrol* 2013;17:51–8.
- 3 Rawal G, Kumar R, Yadav S. ECMO Rescue Therapy in Diffuse Alveolar Haemorrhage: a case report with review of literature. *J Clin Diagn Res* 2016;10:OD10–OD11.
- 4 Pacheco Claudio C, Charbonney E, Durand M, *et al.* Extracorporeal membrane oxygenation in diffuse alveolar hemorrhage secondary to systemic lupus erythematosus. *J Clin Med Res* 2014;6:145–8.
- 5 Yusuff H, Malagon I, Robson K, *et al.* Extracorporeal membrane oxygenation for Life-threatening ANCA-positive pulmonary capillaritis. A review of UK experience. *Heart Lung Vessel* 2015;7:159–67.
- 6 Extracorporeal Life Support Organization (ELSO). Guidelines for adult respiratory failure. <http://www.elso.org/resources/Guidelines.aspx> (accessed 9 Aug 2016).

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