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CASES WITH A MESSAGE

The role of extra-corporeal membrane oxygenation (ECMO) in the treatment of diffuse alveolar haemorrhage secondary to ANCA-associated vasculitis: report of two cases and review of the literature

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Abstract
Diffuse alveolar haemorrhage (DAH) secondary to anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV) is a rare life-threatening condition presenting with severe respiratory failure. The management of AAV-related DAH consists of remission induction immunosuppressive therapy, which requires time to be effective, with significant fatality rates despite appropriate treatment. Extracorporeal membrane oxygenation (ECMO) can support gas exchanges providing the time necessary for immunosuppressive treatment to control the underlying disease in cases refractory to the conventional ventilation techniques. Despite severe preexisting bleeding has been considered a relative contraindication, ECMO has proven to be life-saving in several cases of respiratory failure associated with pulmonary haemorrhage due to various causes, including AAV. We reviewed the clinical presentation and course of two patients affected by AAV-related DAH treated at our Institution between 2012 and 2017, whose management required the use of veno-venous ECMO. We reviewed the current literature on the role of ECMO in the support of these patients. In both patients, ECMO provided life support and allowed disease control, in combination with immunosuppressive treatment. Despite systemic anticoagulation, clinical improvement was achieved without exacerbation of the pulmonary bleeding. We performed a literature review, and summarized available data confirming the effectiveness and safety of ECMO in AAV-related DAH. ECMO has a life-saving role in the management of patients with severe respiratory failure due to ANCA-associated pulmonary capillaritis.

Keywords ANCA-associated vasculitides · Extra-corporeal membrane oxygenation · Diffuse alveolar haemorrhage · Respiratory failure

Introduction

Anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitides (AAV) are a group of systemic disorders characterized by inflammation and necrosis of small-and-medium-size vessels. Although most organs can be affected, pulmonary involvement is one of the most frequent manifestations. Every level of the pulmonary vasculature may be damaged, with a predilection for pulmonary capillaries. The derangement of the alveolar basement membrane resulting from the widespread injury of the pulmonary capillaries promotes the extravasation of red blood cells into the pulmonary

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alveolar spaces. This condition, known as diffuse alveolar haemorrhage (DAH), is one of the most serious complications and one of the strongest predictors of early mortality in the course of AAV [1, 2], with 1-year mortality rate varying between 18 and 50% [3, 4]. Extracorporeal membrane oxygenation (ECMO) is a tool that provides life support in case of severe acute respiratory failure refractory to the conventional ventilation approaches [5, 6]. ECMO was introduced in 1972 for the support of respiratory failure of the newborns and, since then, has been applied to an increasing number of complex conditions [7, 8]. Veno-arterial ECMO (VA-ECMO) is used in cardiac or cardiorespiratory failure, while veno-venous ECMO (VV-ECMO) is employed in respiratory failure without cardiac compromise, offering temporary life support. Recent technological advances have made AAV-related DAH a potential indication for ECMO, even if a certain degree of systemic anticoagulation is required, which represents an issue of concern in case of DAH. Therefore, balancing risks and benefits is crucial, as supporting gas exchanges and sparing time for immunosuppressive agents to explicate their effect are counterbalanced by the need for anticoagulation in the course of a major bleeding.

Methods and search strategy

Here, we describe the clinical presentation and management of two patients, affected by AAV, who presented with severe respiratory failure refractory to the conventional ventilation techniques treated at Policlinico San Matteo, Pavia, in 2012 and 2017, respectively. Written informed consent was obtained from involved patients. We performed a review of the available literature concerning the role of ECMO in the treatment of AAV-related DAH. We searched PubMed for English-language sources, from inception until January 2018, combining the following keywords: extracorporeal membrane oxygenation and ANCA-associated vasculitides or vasculitis. We identified 20 cases of DAH secondary to AAV supported with ECMO, six of which were excluded due to lack of complete clinical data.

Case descriptions

Case 1

A 45-year-old woman with a 20-day history of polyarthralgia developed acute dyspnea and hemoptysis. She was conducted to the Accident and Emergency Department (A&E) and admitted to the Division of Infectious Diseases. She then developed fever > 38 °C and progressive anemia, with raised acute-phase reactants. Laboratory findings at presentation and during follow-up are shown in Table 1. Although antimicrobial therapy was initiated, the patient's general conditions worsened with the onset of acute respiratory failure. A chest CT scan showed diffuse ground-glass opacities suggestive of acute respiratory distress syndrome (ARDS) (Fig. 1a). The blood gas exchange parameters were remarkably impaired (pH 7.25, PaO2 49.5 mmHg, PaCO2 63.7 mmHg), and thus, the patient was transferred to the Intensive Care Unit (ICU), intubated, and mechanically ventilated. Bronchial fibroscopy (BFS) revealed active bronchial bleeding, with negative bronchoalveolar lavage (BAL) fluid microbiological tests. Further anemization required the transfusion of 3 units of RBC. For persistent hypoxemia refractory to mechanical ventilation, a full VV-ECMO support was initiated. Immunological tests showed c-ANCA (PR3) positivity (Table 1) and rose suspicion of AAV-related DAH. Therefore, the patient was treated with methylprednisolone (MP) pulses (1 g intravenously/day on 3 consecutive days), plasma exchange (PE), and cyclophosphamide (CyC) pulses. Chest CT scan performed after 8 days demonstrated progressive improvement of lung transparency and resolution of the alveolar bleeding (Fig. 1b). Regular blood gas estimation revealed gradual improvement of respiratory function (Fig. 2) and ECMO support was stopped after 6 days. On day 13, the patient was transferred to our Rheumatology Unit and was discharged from hospital care 23 days later. She completed the remission induction treatment with 6 monthly CyC pulses (1500 mg/month intravenously). After remission achievement and steroid tapering, maintenance immunosuppressive treatment with azathioprine 2 mg/kg/day was started. Steroid treatment and azathioprine were withdrawn after 2 and 3 years, respectively, with clinical stationarity and normal blood acute-phase proteins, despite persistent c-ANCA (PR3)-positivity (Table 1). A recent CT chest scan showed complete resolution of pathological findings (Fig. 1c).

Case 2

In September 2015, a 45-year-old man was admitted to our Rheumatology Unit reporting a 30-day history of ear, nose, and throat (ENT) manifestations, lower limbs oligoarthritis, and tinglings. Laboratory tests and urine sediment analysis at presentation and during follow-up are shown in Table 1. C-ANCA (PR3) antibodies were detected. Electroneurography showed abnormal pattern suggestive of minimal axonal sensorimotor polyneuropathy. Granulomatosis with polyangiitis (GPA) was diagnosed and treatment with prednisone 37.5 mg/day and methotrexate 15 mg/week was initiated, with achievement of clinical remission and ANCA negativisation. Prednisone was gradually tapered. In February 2017, after 1 year of stable disease, the patient presented with low-grade fever, arthralgia, and recurrent ENT symptoms. Laboratory findings revealed increased acute-phase reactants and

Table 1 Laboratory findings and urine sediment analysis of patients affected by AAV at disease onset and during follow-up

	Patient 1		Patient 2			
	Disease onset with DAH	Last follow-up (5 years)	Disease onset	Renal flare	Pulmonary flare with DAH	Last follow-up (14 months)
Hb (g/dl)	6.5	14.3	11.2	11.6	6.5	14.9
Total and differential leucocyte count (10^3/μL)	19.6 (N 17.2, L 1.8)	4.9 (N 3.6, L 1.1)	13.9 (N 11.2, L 1.0)	14.0 (N 13.4, L 0.4)	12.3 (N 11.3, L 0.2)	10.5 (N 8.5, L 0.9)
Platelet count (10^3/μL)	470	323	462	274	181	232
ESR (mm/h)	101	19	77	96	90	29
CRP (mg/dl)	10.4	0.3	14.4	22.5	8.7	0.1
Creatinine (μmol/L)/GFR (ml/min)	66.3/96.3	58.3/103	77.8/102.3	672/7.7	613/8.6	203.4/32.6
ANCA status (IFI, EIA title)	c-ANCA 1:640 PR3 101 U/ml	c-ANCA 1:320 PR3 15 U/ml	c-ANCA 1:320 PR3 12 U/ml	c-ANCA 1:320 PR3 22 U/ml	c-ANCA 1:320 PR3 7.7 U/ml	Negative
Proteinuria (mg/24 h)	300	< 150	400	1700	2000	1200
Urine sediment analysis	10 Dysmorphic RBC/HPF, no casts	No cells or casts	No cells or casts	50 Dysmorphic RBC/HPF, several RBC casts	30 Dysmorphic RBC/HPF, several RBC casts	No cells or casts

DAH diffuse alveolar haemorrhage, *Hb* haemoglobin, *ESR* erythrosedimentation rate, *CRP* C-reactive protein, *GFR* glomerular filtration rate, *N* neutrophils, *L* lymphocytes, *IFI* indirect immunofluorescence, *EIA* enzyme immunoassay, *PR3* anti-proteinase 3, *RBC/HPF* red blood cells/high power field

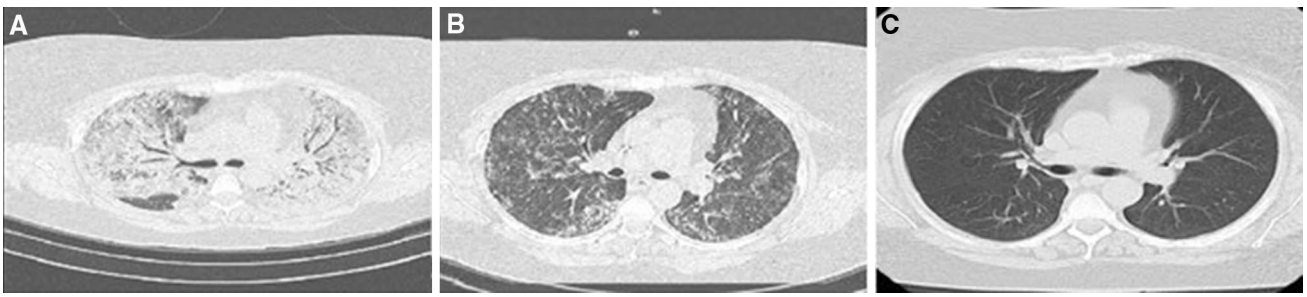

Fig. 1 **a, b, c** HRCT lung findings at disease onset, after 8 days in ICU, and after 5 years

signs of renal involvement (Table 1). The patient was admitted to our Rheumatology Unit. Blood chemistry showed further worsening of renal function associated with c-ANCA (PR3) positivity (Table 1) and urinary sediment analysis was suggestive of acute glomerulopathy (Table 1). MP pulse therapy (1 g intravenously/day on 3 consecutive days) tapered to oral MP 1 mg/kg/day was started, followed by intravenous CyC (12,5 mg/kg according to EUVAS scheme [9, 10] adjusted for glomerular filtration rate [11]). Hemodialytic replacement therapy was required. Renal biopsy confirmed pauci-immune rapid progressive glomerulonephritis (RPGN). Pulmonary high-resolution CT (HRCT) showed numerous, bilateral nodules localized to the upper and lower pulmonary lobes, consistent with pulmonary involvement of GPA. For the collateral finding of thrombosis of the right inner jugular vein, and site of temporary central venous catheter (CVC), anticoagulation was started. The patient was discharged and continued renal replacement therapy and CyC pulses on the Day-care ward. A few hours after the fourth CyC infusion, the patient was conducted to A&E reporting nausea and hematemesis. On admission, he developed worsening type II respiratory failure (pH 7.28, PaO2 57.8 mmHg, PaCO2 56.3 mmHg), progressive anemia, and acute on chronic kidney disease (Table 1). Two units of RBC were transfused. Chest CT scan revealed diffuse pulmonary consolidations, suggestive of massive alveolar haemorrhage (Fig. 3a). The patient was intubated, transferred to the ICU, and mechanically ventilated. BFS showed copious

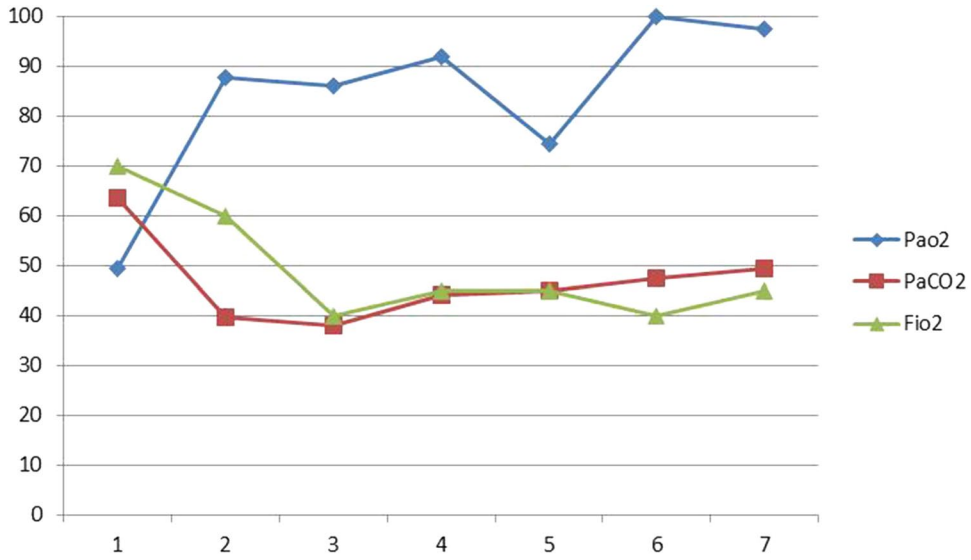

Fig. 2 Progression of pulmonary gas exchange during days of permanence on ECMO

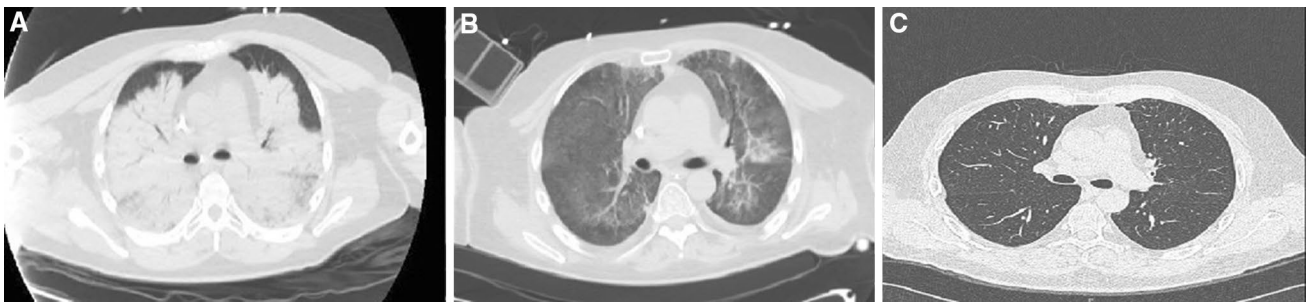

Fig. 3 **a, b, c** HRCT lung findings at DAH onset, after 17 days in ICU, and after 6 months

lower airways bleeding. Because of further worsening of gas exchange, a full VV-ECMO support was started, with quick restoration of the patient's oxygen saturation. Considering the anti-PR3-positivity (Table 1) and negative BAL microbiological investigations, the suspicion of GPA-related DAH was confirmed and the patient was treated with MP pulse therapy (1 g intravenously/day on 3 consecutive days), followed by rescue therapy with rituximab (RTX) (375 mg/m^2/week on 4 consecutive weeks). Hemodialytic sessions were maintained on a regular basis. During ECMO support, respiratory function significantly improved (Fig. 4) even though the patient developed subcutaneous emphysema and an abdominal hematoma successfully treated with percutaneous thrombin injection. On day 14, ECMO was discontinued. A pulmonary HRCT performed after 17 days revealed gradual improvement of pulmonary ventilation and reabsorption of the alveolar haemorrhage (Fig. 3b). On day 32, the patient was transferred to our Unit and discharged 26 days later. In the following weeks the patient's general conditions remarkably improved and good pulmonary function was restored. Haemodyalitic sessions were withdrawn with stable renal function (Table 1). A chest CT scan performed in October 2017 revealed the complete resolution of the pulmonary consolidations, with fine residual fibrotic striae (Fig. 3c). In November 2017 maintenance immunosuppressive treatment with rituximab (500 mg/6 months) was started, with persistent clinical remission and ANCA negativity (both IIF and EIA).

Discussion

Hereby, we described two patients affected by severe respiratory failure secondary to AAV-related DAH, whose prognosis would have been poor without the use of ECMO. In both patients, ECMO provided time for life-saving treatments to explicate their effect in halting the pathologic process. No exacerbation of alveolar haemorrhage occurred and the active bleeding stopped after initiating ECMO. With the conventional ventilation, neither of them was likely to survive long enough for the immunosuppressive therapy to be effective.

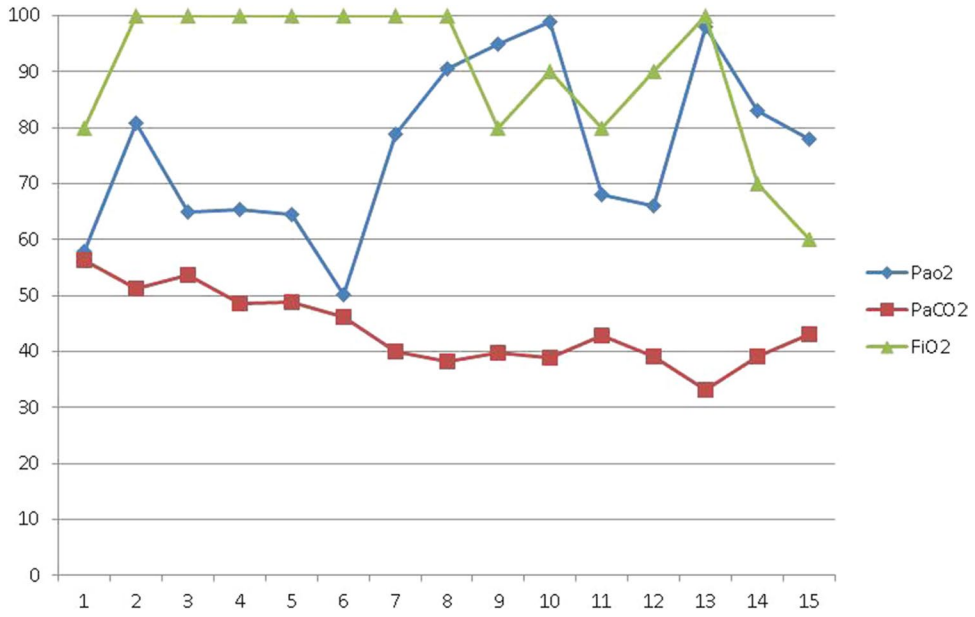

Fig. 4 Progression of pulmonary gas exchange during days of permanence on ECMO

DAH is a life-threatening condition that can complicate the course of AAV with a protean clinical presentation, ranging from acute respiratory failure to a more subtle course. Although most patients develop a certain degree of hemoptysis, this symptom is missing in about one-third of cases. Constitutional symptoms, cough, dyspnea, and chest pain may occur [12], whereas fall of haemoglobin is a common laboratory finding [13]. The co-existence of DAH and acute glomerulonephritis is typically defined as pulmonary renal syndrome. Although radiological findings are nonspecific and variable with time of onset of the haemorrhage, imaging studies, especially pulmonary HRCT, may provide additional information. Typical patterns can range from lobular or lobar areas of ground-glass opacities to predominant consolidation as a consequence of alveolar filling. Throughout the resolution of the acute haemorrhage, interlobular septal thickening superimposed on areas of ground-glass opacity may give rise to a "crazy-paving" pattern [14]. Nevertheless, additional laboratory tests and bronchoscopy with BAL are necessary, due to the low specificity of symptoms and clinical–radiological signs. BFS with BAL is mandatory to confirm the intra-alveolar haemorrhage and rule out infections or bleeding lesions in the upper airways. An increasingly haemorrhagic appearance of consecutive BAL aliquots and BAL iron staining showing more than 20% hemosiderin-laden macrophages (HLM) are highly suggestive for DAH [15]. DAH represents the main cause for hospitalization and ICU admission in AAV [16, 17]. In a previous case series, we described 90 patients affected by AAV, 10 of whom experienced a life-threatening disease onset manifestation leading to diagnosis in the ICU setting [18]. Cardio-pulmonary acute involvement was the main cause for ICU admission, accounting for 70% of cases, with DAH representing the leading cause of respiratory failure. Treatment of AAV-related DAH should be guided by the recommendations for the management of new onset organ-threatening or life-threatening disease. Remission induction schemes proposed by the recently updated EULAR/ERA-EDTA recommendations suggest a combination of high-dose glucocorticoids (GC) and either CyC or RTX [19]. In case of a major relapse of organ-threatening or life-threatening AAV, treatment as per new disease is recommended.

Although immunosuppressive treatment has significantly increased the survival rate in patients affected by AAV, supportive approaches for complications affecting vital organs may be necessary. ECMO is an advanced circulatory and ventilatory support system used as salvage therapy for patients with refractory hypoxemia and/or cardiac failure when the conventional treatment fails [20]. During severe respiratory failure unresponsive to the conventional mechanical ventilation, ECMO can be applied, preventing severe hypoxia and removing carbon dioxide until the restoration of the pulmonary function. Recent developments in ECMO technology [5, 21] have reduced complications associated with this procedure, safely extending its employment to other life-threatening conditions, including trauma, cardio-pulmonary resuscitation, and interstitial lung diseases [7, 8]. Despite the increased application of ECMO for severe respiratory failure over the last years, its effectiveness is still controversial. In a recent international, randomized trial involving 249 patients presenting with severe ARDS (mainly due to infectious causes), 60-day mortality was not significantly lower with ECMO compared with the conventional treatment, a strategy which included crossover to ECMO in case of refractory hypoxemia [22]. Further studies are needed to clarify the effective role of ECMO in the support

of severe respiratory failure unresponsive to mechanical ventilation. Because of the rarity and the high mortality rate of DAH secondary to AAV, the evidence for the use of ECMO in this condition is restricted to a small number of case reports [23–43]. We performed a review of the current literature concerning the role of ECMO in the management of AAV-related DAH. Fourteen case descriptions provided with comprehensive clinical data are summarized in Tables 2 and 3. DAH occurred at disease onset in all cases. ANCA were positive in all cases, anti-PR3/anti-MPO positivity: 78.6%/21.4%. As soon as life-threatening AAV was suspected, remission induction therapy with a combination of high-dose GC and immunosuppressive agents (CyC or RTX) was started in 13 cases (92.8%). Four patients (28.6%) also received adjuvant treatment with intravenous immunoglobulin. Twelve patients (85.7%) underwent PE and nine (64.3%)

Table 2 Clinical features of patients affected by DAH secondary to AAV and supported with ECMO

Author	Sex	Age	ANCA specificity (EIA)	New onset or disease flare	Medical treatment
Hernandez et al. [27]	Male	13	PR3	New onset	GC, IVIG
Rosengarten et al. [28]	Female	27	PR3	New onset	GC, Cyc
Ahmed et al. [29]	Female	26	PR3	New onset	GC, CyC, IVIG
Agarwal et al. [30]	Male	16	MPO	New onset	GC, CyC
Balasubramanian et al. [31]	Male	53	PR3	New onset	GC, CyC
Di Maria et al. [32]	Male	13	MPO	New onset	GC, CyC, RTX
Guo et al. [34]	Female	51	MPO	New onset	GC, CyC, IVIG
Joseph and Charles [36]	Male	13	PR3	New onset	GC
Barnes et al. [37]	Female	50	PR3	New onset	GC, CyC
Hohenforst et al. [39]	Female	65	PR3	New onset	GC, CyC
Yusuff et al. [40]	Female	23	PR3	New onset	GC, CyC
	Male	27	PR3	New onset	GC, RTX, IVIG
Rawal et al. [41]	Male	28	PR3	New onset	GC, Cyc
Vanoli et al. [42]	Male	33	PR3	New onset	GC, CyC
Present paper	Female	45	PR3	New onset	GC, Cyc
	Male	47	PR3	Disease flare	GC, RTX

EIA enzyme immunoassay, *MPO* myeloperoxidase, *PR3* anti-proteinase 3, *GC* glucocorticoids, *Cyc* cyclophosphamide, *RTX* rituximab, *IVIG* intravenous immunoglobulin

Table 3 Use of other supportive approaches and ICU course of patients affected by DAH secondary to AAV and supported with

Author	Plasma exchange	Haemodialyses	ECMO support duration (days)	ECMO-related complications
Hernandez et al. [27]	Yes	No	15	No
Rosengarten et al. [28]	No	Yes	6	No
Ahmed et al. [29]	Yes	Yes	14	Hemothorax in the site of pneumothorax chest tube
Agarwal et al. [30]	Yes	No	7	No
Balasubramanian et al. [31]	Yes	Yes	7	Asymptomatic heparin-induced thrombocytopenia
Di Maria et al. [32]	Yes	Yes	5	No
Guo et al. [34]	Yes	Yes	13	Mild hematuria
Joseph and Charles [36]	Yes	Yes	5	No
Barnes et al. [37]	Yes	Yes	6	No
Hohenforst et al. [39]	Yes	Yes	10	No
Yusuff et al. [40]	No	No	12	No
	Yes	Yes	10	No
Rawal et al. [41]	Yes	No	21	No
Vanoli et al. [42]	Yes	No	Not available	No
Present paper	Yes	No	6	No
	No	Yes	14	Abdominal hematoma

required renal replacement therapy because of RPGN. The mean duration of ECMO support was 10.1 ± 4.8 days, in line with our two case descriptions (respectively 6 and 14 days). All patients survived and were discharged from hospital care. The patients described above did not receive the same protocol of CyC. In case 1, diagnosed and treated few years previously, remission induction regimen was represented by 6 monthly CyC pulses (1500 mg/month) [44]. Nevertheless, cumulative dose of CyC was similar compared to EUVAS scheme and this approach resulted in an excellent clinical response, demonstrated by the persistence of sustained drug-free remission. In case 2, our patient developed DAH following CyC administration. Due to the concomitant kidney involvement, AAV-related DAH was suspected and promptly treated. Nevertheless, differential diagnosis should take into account the very rare occurrence of CyC-induced lung toxicity, which has been anecdotally reported [45, 46].

Despite its life-saving potential, ECMO enhances an inflammatory response, resulting in a pro-thrombotic state, which requires anticoagulation to prevent thromboembolism developing in the non-endothelial surfaced circuit. Bleeding is the main complication in patients undergoing ECMO. Risk factors include constant anticoagulation therapy and coagulopathy secondary to clotting factors consumption [47–49]. The use of heparin-coated ECMO has proved to reduce the daily blood loss, the amount of RBC infusion, and the intravenous heparin dose [21]. Although ECMO has no absolute contraindications, conditions with a significant risk of bleeding or preexisting severe bleeding have been considered relative contraindications. Therefore, balancing harms and benefits of single patient is crucial. On one hand, the occurrence of DAH may represent an issue of concern for ECMO application, as systemic heparinization may exacerbate the pulmonary bleeding; on the other hand, sparing time for the immunosuppressive treatment to be effective can be life-saving in the course of AAV-related DAH. Moreover, ECMO may explicate a direct beneficial effect during DAH, as it allows a significant decrease in ventilator flow rate. Notwithstanding, with the exception of a patient who developed hemothorax in the site of a chest tube inserted for pneumothorax and a case of asymptomatic heparin-induced thrombocytopenia, no bleeding events occurred among AAV-related DAH requiring ECMO reported in the literature. In one of our cases, the course in ICU was complicated by an abdominal hematoma successfully treated with percutaneous thrombin injection. Our cases demonstrate how a prompt referral by intensivists and A&E physicians to specialist hospitals to allow the early initiation of ECMO can dramatically improve the clinical outcome.

Conclusions

DAH is a life-threatening condition requiring prompt immunosuppressive treatment, which, however, needs time to explicate its effect. ECMO can support gas exchanges, providing the time necessary for induction immunosuppressive treatment to control the underlying disease. In our case series, ECMO supported the respiratory function, permitting the management of pulmonary bleeding, the improvement of radiologic findings, with consequent weaning of the extracorporeal circulation and extubation. No life-threatening bleeding events occurred during ECMO. Although ECMO is a highly invasive procedure with a significant risk of bleeding complications, it should be considered in patients with AAV-related DAH when the conventional mechanical ventilation has failed.

Compliance with ethical standards

Conflict of interest The authors declare they have no conflict of interest.

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