Management and outcome of immune-mediated diffuse alveolar hemorrhage: a single centre case series

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Dear Editor,

Diffuse alveolar hemorrhage (DAH) is a clinical syndrome characterized by alveolar bleeding that can happen as a severe complication of immune-mediated diseases with a high mortality rate[1,2]. Treatment comprises supportive care and addressing the underlying disease. High-dose glucocorticoids (GC) and cyclophosphamide (CYC) or rituximab (RTX) remain the standard of care for immune-mediated DAH (IM-DAH)[2,3]. The role of intravenous immunoglobulin (IVIg) and plasma exchange (PLEX) is controversial[3,4].

Our aim is to describe the treatment approach and outcomes in IM-DAH in clinical practice.

A retrospective single-centre observational study was conducted in patients admitted to a tertiary rheumatology centre between 2005 and 2023 with IM-DAH. Data were retrieved from medical records. A descriptive analysis was performed with IBM® SPSS® Statistics, version 27.0, and data are presented as absolute and relative frequencies.

Twelve cases of IM-DAH were identified, corresponding to ten patients. Their demographics, clinical characteristics, and management are presented in Table I.

IM-DAH was diagnosed by bronchoalveolar lavage (BAL) in nine cases. In three cases (one of them a relapse previously diagnosed with BAL), the diagnosis was made clinically, based on the presence of new pulmonary infiltrates and haemoptysis or a drop in haemoglobin without an alternative explanation. The median hospital stay was 17 days (IQR 27), with intensive care unit admission in seven cases and a median stay of 4 days (IQR 12).

Half of the patients (*n*=5) had the diagnosis of systemic lupus erythematosus (SLE), three of them with secondary antiphospholipid syndrome (APS), and the other five had anti-neutrophil cytoplasmic antibodies associated vasculitis (AAV). DAH was the presenting manifestation in six patients (60%), five of them with AAV and one with SLE and macrophage activation syndrome (MAS).

All episodes were treated with high doses of oral prednisolone (1mg/kg/day) with gradual tapering, and 83.3% (*n*=10) received prior methylprednisolone pulses (500mg-1g/day; 3-5 days). Nine episodes were treated with CYC associated with GC.

Three cases did not receive CYC or RTX due to infectious risk or documented infection – patient 5) developed severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) and cytomegalovirus (CMV) infection; 7) had hypogammaglobulinemia and splenectomy and relapsed one year later following SARS-CoV2 infection for which was treated only with GC (methylprednisolone 1g/day 3 days, followed by prednisolone 1mg/kg/day).

IVIg was administered in three cases: patient 7) due to infectious risk associated with hypogammaglobulinemia and splenectomy; 8) to achieve a faster response for surgical intervention; and 10) due to clinical worsening under CYC.

PLEX was used in six cases: patient 1) and 8) due to clinical worsening and proteinuria; 5) due to rapidly progressive glomerulonephritis; 7) as add-on to IVIg in a patient with hypogammaglobulinemia and splenectomy; and 9) for severe disease with MAS before and after relapse – the patient relapsed prior to discharge whilst on prednisolone 1mg/kg/day and was retreated with CYC and PLEX.

Nine patients survived after a one-year follow-up. One patient died one month after diagnosis due to severe infection with SARS-CoV2 and CMV.

IVIg was only administered to patients with SLE and/or APS, and half of the patients treated with PLEX had suspected kidney involvement. IVIg and PLEX were most used in patients admitted to the intensive care unit as add-on therapies or, less commonly, when other immunosuppression was contraindicated.

Two patients with APS were under anticoagulation with warfarin, the third was only under anti-aggregation, since she had obstetric APS. Antibiotics were administered in ten episodes due to suspected concurrent infection, which can be challenging to exclude.

In clinical practice, IVIg may have a role as first-line and/or bridging therapy due to its lower infectious risk in AAV and SLE/APS.[5] Although PLEX is not recommended for AAV-associated DAH, it may have a role in patients with a high risk of progression to chronic kidney disease, according to the MEPEX trial[3,4,6].

This study is limited by its retrospective design, small sample size, and single-center setting. Future prospective studies are needed to further clarify the role of IVIg and PLEX in the treatment of IM-DAH.

The combination of GC and CYC was the most used treatment regimen, with a favourable clinical response. CYC was preferred over RTX due to its rapid onset of action. While the role of PLEX and IVIg in AAV and SLE/APS-associated DAH remains uncertain, these therapies may be considered as a second-line or as add-on, particularly in refractory or critically ill patients[3-5,7-8].

Tables and Figures

Table I – Demographic and clinical characteristics of DAH patients and management of each DAH episode.

ID	Sex	Race	Tobacco exposure	Diagnosis	Age diagnosis (years)	Age DAH (years)	DAH as inaugural manifestation	Symptoms	Haemoglobin drop	Other relevant manifestations	Oral GC	IV GC	CYC	PLEX	IVIg	IMV	ICU	Antibiotics	1-year survival
1	F	White	X	EGPA	70	70	✓	dyspnoea, haemoptysis, cough	✓	Polyneuropathy; Proteinuria	✓	✓	✓	✓	X	✓	✓	✓	✓
2	M	Asian	X	GPA	29	29	✓	dyspnoea, haemoptysis, cough	✓	RPGN	✓	✓	✓	X	X	X	✓	✓	✓
3	M	White	✓	GPA	52	52	✓	asymptomatic	X	Mononeuropathy multiplex	✓	✓	✓	X	X	X	X	X	✓
4	F	White	X	GPA	48	48	✓	fever, dyspnoea, haemoptysis, cough	-		✓	✓	✓	X	X	X	✓	✓	✓
5	F	White	X	MPA	82	82	✓	asymptomatic	✓	RPGN	✓	✓	X	✓	X	X	X	✓	X
6	F	Black	X	SLE+APS	20	26	X	fever, dyspnoea	✓		✓	X	✓	X	X	X	X	X	✓
7	F	White	✓	SLE+APS	34	52	X	fever, dyspnoea	✓		✓	✓	X	✓	✓	X	✓	✓	✓
						52	X	fever, dyspnoea	✓	SARS-CoV2 infection	✓	✓	X	X	X	X	X	✓	✓
8	M	White	✓	SLE+APS	38	38	X	fever, dyspnoea, haemoptysis, cough	✓	Proteinuria	✓	✓	✓	✓	✓	✓	✓	✓	✓
9	F	White	X	SLE	26	26	✓	fever	✓	MAS	✓	✓	✓	✓	X	✓	✓	✓	✓
						26	X	dyspnoea, haemoptysis, cough	✓		✓	✓	✓	✓	X	X	X	✓	✓
10	F	Black	X	SLE	26	28	X	fever, dyspnoea, chest pain, haemoptysis, cough	✓	Proteinuria	✓	X	✓	X	✓	X	✓	✓	✓

ID, identification; *DAH,* Diffuse alveolar hemorrhage; *GC,* oral glucocorticoids (oral prednisolone 1mg/kg/day); *IV GC*, intravenous glucocorticoids (methylprednisolone); *CYC*, cyclophosphamide; *PLEX*, plasma Exchange; *IVIg*, intravenous immunoglobulin (2g/kg); *IMV*, invasive mechanical ventilation; *ICU*, intensive care unit; *F*, Female; *M*, Male; ✓, yes; ***X***, no; *EGPA,* eosinophilic granulomatosis with polyangiitis; *GPA,* granulomatosis with polyangiitis; *MPA*, microscopic polyangiitis; *SLE*, systemic lupus erythematosus; *APS*, anti-phospholipid syndrome; *RPGN*, rapidly progressive glomerulonephritis; *SARS-CoV2*, severe acute respiratory syndrome coronavirus 2; *MAS*, macrophage activation syndrome.

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