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Letter to the Editor (Other)

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Pulmonary haemorrhage in ANCA-associated vasculitis

SIR, Pulmonary haemorrhage (PH) is a potential life-threatening feature of ANCA-associated vasculitis (AAV) [microscopic polyangiitis (MPA), WG and Churg–Strauss syndrome (CSS)] [1]. We studied patients presenting with PH in the context of AAV to ascertain the outcome of PH at 4 weeks. Patients who had AAV and PH between January 2002 and December 2008 were identified from the departmental database and their case notes were reviewed. PH was defined as haemoptysis and X-ray showing bilateral, diffuse parenchymal pulmonary infiltrates [2] and falling haemoglobin. All included patients fulfilled either the ACR criteria or the Chapel Hill Consensus Conference definitions for AAV using the European consensus classification algorithm [3]. The Birmingham vasculitis activity score [4] at presentation was calculated retrospectively. Outcome at 4 weeks was categorized as either resolution of PH (cessation of haemoptysis, clear chest X-ray and stable haemoglobin) or death.

Nine patients (WG, six; MPA, two; and CSS, one) were included (Table 1); all had new diagnosis of AAV. Haemoptysis and falling haemoglobin [mean (S.D.) haemoglobin at nadir, 8.81 g/dl (1.42); mean (S.D.) fall in haemoglobin, 4.16 g/dl (1.6)] were among the presenting features in all patients. There was no evidence of anti-glomerular basement membrane (anti-GBM) disease. Six patients had abnormal renal function at presentation. (Creatinine range 125–249 μmol/l in two; 250–500 μmol/l in two; >500 μmol/l in one; and rise in creatinine of >30% in one.)

Eight patients received i.v. cyclophosphamide, 15 mg/kg up to a maximum of 1 g, with i.v. methylprednisolone (i.v. MPS) 1 g for three consecutive days, with a reducing dose of daily oral prednisolone (initial dose 1 mg/kg/day; maximum dose 60 mg) as induction therapy. One patient was pregnant and was treated with oral azathioprine (AZA) and i.v. MPS. Five patients (56%) underwent sequential therapeutic plasmapheresis with 5% human albumin solution as replacement fluid and 2 U of fresh frozen plasma at the end of plasmapheresis. Three patients required haemodialysis.

At 4 weeks, PH had resolved in six (67%) patients, three of whom had plasmapheresis (Table 1). Three patients died of severe PH in the first 4 weeks; in one of these, there was a delay in the diagnosis and immunosuppressive therapy was commenced only on Day 9 of hospital admission, when respiratory failure necessitated mechanical ventilation. One patient (Patient 5) remained dialysis dependent and developed cyclophosphamide-induced cytopenia 8 weeks after the onset of PH. The patient died due to infection (*Clostridium difficile* and Norvovirus) 13 weeks after presentation. In this patient, PH had resolved by 4 weeks. Long-term follow-up [range 6 months (Patient 9) to 6.5 years (Patient 1)] of five surviving patients has shown no relapse of PH.

In the present as well as the previous series, mortality was higher in patients requiring mechanical ventilation, which could be due to severe PH and an underlying vasculitic process; ventilation-induced lung injury; or increased susceptibility to infections [5–7]. However, some patients with PH were successfully weaned off ventilators in our and previous series: this suggests that early appropriate treatment may still be able to dramatically improve outcome in some of the patients with PH. Non-invasive continuous positive airway pressure ventilation could be used first in conscious and cooperative patients, provided the required oxygenation can be maintained; this was successfully used in two patients in our study.

In a previous study, 12 (86%) out of 14 patients had plasmapheresis as adjunctive therapy to induction therapy with prednisolone (in 57% i.v. MPS) and daily cyclophosphamide in 13 out of 14 patients (orally in the majority). Five (36%) patients died in this study in the first four weeks; it is unclear how many of them had plasmapheresis [5]. In another study, remarkably, PH resolved in all 20 patients who had plasmapheresis as adjunctive therapy to induction by i.v. cyclophosphamide and i.v. MPS [8]. In our study, PH resolved in three out of five patients who had plasmapheresis and also in three out of four patients who did not have plasmapheresis. Post-therapy ANCA levels were not measured in previous studies [5, 8]; in our study, post-therapy ANCA levels fell in patients irrespective of plasmapheresis. Therefore, when considered together, these three studies underline the need for identification of patients with PH where adjunctive therapy with plasmapheresis would be beneficial. A recent study has confirmed the benefit of plasmapheresis compared with i.v. MPS in AAV patients presenting with creatinine >500 μmol/l in renal survival at 3 months [9]; such thresholds for patients with PH need to be defined.

PH in AAV is a life-threatening entity, often with a fulminant course if untreated. Speed in making a diagnosis and instituting therapy for AAV is essential, especially in the face of life-threatening PH or rapidly progressive glomerulonephritis [10]. Our study highlights the importance of prompt diagnosis and initiation of immunosuppressive therapy with prednisolone and cyclophosphamide. The role of plasmapheresis as adjunctive therapy remains to be established.

Rheumatology key message

- Prompt immunosuppressive therapy is important to improve the outcome of PH in ANCA-associated vasculitis.

LETTER

Table 1 Demographics, clinical features and outcome of PH at 4 weeks

Patient number	Diagnosis	Age, years/gender	Hb at nadir, g/dl	ANCA[a], U/ml	BVAS	Ventilation, days	PlasmaX, *n*	ANCA[b], U/ml	Outcome
1	WG	45/male	9.3	c, PR3 18	25	3[c]	NA	2	Resolved
2	WG	21/male	6.4	c, PR3 100	25	1	NA	ND	Died
3	WG	32/female	9.1	c, PR3 21	14	NA	NA	6	Resolved
4	WG	34/female	9.9	c, PR3 255	24	NA	NA	85	Resolved
5	MPA	80/female	7.6	p, MPO 375	20	NA	10	65	Resolved[d]
6	WG	38/male	8.9	c, PR3 100	38	1	1	ND	Died
7	MPA	76/female	10.9	p, MPO 140	24	10	6	ND	Died
8	WG	60/female	7.4	c, PR3 120	22	8	12	7	Resolved
9	CSS	80/male	9.8	p, MPO 624	21	7[c]	7	159	Resolved

[a]At presentation; [b]at 4 weeks; [c]non-invasive ventilation; [d]died at 13 weeks. PlasmaX: plasmapheresis; NA: not applicable; ND: not done; BVAS: Birmingham Vasculitis Activity Score; c: cytoplasmic; p: perinuclear; PR3: proteinase3; MPO: myeloperoxidase; Hb: haemoglobin.

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