The Effects of Plasma Exchange on Diffuse Alveolar Hemorrhage in Severe Vasculitis – A Case Study

ABSTRACT

Introduction: Rapidly progressive glomerulonephritis (RPGN) and widespread alveolar haemorrhage define ANCA associated vasculitis (AAV), a rare life-threatening illness (DAH).
Case presentation: An elderly female came with lower limb weakness and oliguria, hadfeatures suggestive of RPRF and fluid overload. She developed hemoptysis with respiratory failure despite haemodialysis and intravenous steroids. The diagnosis of patients was pulmonary renal syndrome– DAH in the setting of ANCA, and based on the HRCT chest and positive p-ANCA report.She had excellent response to intravenous pulse steroids, cyclophosphamide and exchange of plasma received.

Conclusion: On the basis of observation showed importance of immediate intervention inpotentially fatal disease DAH in AAV.

Key words: ANCA, AAV-ANC , DAH, PE, RPGN.

INTRODUCTION

Pulmonary rnal syndrome (PRS), antineutrophil cytoplasmic antibody (ANCA)-associated small vessel vasculitis (ASVV), cryoglobulinemia, systemic lupus erythematosus, environmental factors, and certain drugs are among the causes of pulmonary renal-syndrome (PRS), which is characterised by a combination of diffuse alveolar haemorrhage (DAH) and rapidly progressive glomerulonephritis (RPGN 1. Around 70% of PRS cases are caused by AAV, which can be caused by microscopic polyangiitis (MPA), Wegener's granulomatosis, and Churg-Strauss disease. Antiproteinase-3 (anti-PR3, c-ANCA) and antimyeloperoxidase (anti-MPO, p-ANCA) antibodies, both of which have been linked to ASSV pathophysiology, are present in 70–90% of patients and help in diagnosis2,3. Because the commercial serologic investigation proved positive, our current patient may be placed into a recognised subgroup. However, a renal biopsy could not be performed for confirming the diagnosis. PRS was diagnosed based on clinical manifestations and serological reports but without histopathological findings. [4]

CASE REPORT

60 year old lady was admitted to our hospital with moderate grade fever off and on since past 4 months. For last 15 days, she had weakness in both legs with tripping while walking, with tingling and numbness. She had reduced urine output since 5 days. She denied any history of rash, cutaneous nodules, arthritis or hemoptysis. A month prior to her admission she had visited general practitioner locally, had normal serum creatinine (0.98 mg/dl) and

was given symptomatic treatment. She had pulmonary tuberculosis 7 years back and she took complete course of anti-tuberculosis treatment. On admission, a physical examination revealed pale conjunctiva, body weight of 45.0 kg, and body temperature of 36.7℃, pulse rate of 80 beats/min, blood pressure of 162/94 mmHg and bilateral 2+ pitting edema in lower extremities. Her percutaneous oxygen saturation of 96% on atmospheric air with a respiratory rate of 12-16 breath/min, and her Birmingham Vasculitis Activity Score was 24.

Her systemic examination for respiratory, cardiovascular & abdomen was unremarkable. Neurological examination was suggestive of lower motor neuron involvement in lower limbs with grade 3 power distally and sluggish deep tendon reflexes in both lower limbs. She suffered sensory loss in her lower limbs below the knees and patchy sensory loss in her upper limbs. There was no respiratory muscles involvement. Cranial nerves and coordination were normal. As shown in Table, on admission the serum creatinine level was 7.6 mg/dL, metabolic acidosis and normocytic anemia. Immediately she was started on hemodialysis support. Chest x-ray showed a fibrotic patch in right upper zone. Her sputum for Acid fast bacilli & Quantiferon gold were negative & ruled out active tuberculosis.

An echocardiogram revealed an ejection fraction of 62%, type I diastolic dysfunction, mild to moderate mitral regurgitation without evidence of tamponade or pulmonary artery hypertension. Her ultrasound abdomen revealed bilaterally normal size kidneys with raised echotexture bilaterally. Urinary findings and increasing loss of renal function were used to diagnosis rapidly progressive glomerulonephritis (RPGN), thus we scheduled a percutaneous renal biopsy once her overall state improved.

We ruled out multiple myeloma. A nerve conduction study and electromyography were performed which revealed severe sensori-motor neuropathy. It was asymmetrical, mixed type, involving lower limbs more than upper limbs. MRI Lumbosacral spine revealed left subarticular annular tear and broad based central disc protrusion at L4-L5 level; however being trivial, was not contributing to the neurological deficit. Her blood and urine culture showed no growth. 3rd Day of admission: In addition to hemodialysis and maintaining euvolemia, intravenous methylprednisolone pulse therapy was administered 500mg every 24 hours.

On next day she had worsening of her respiratory condition in the form of dyspnea, hypoxia and a bout of hemoptysis. By this time, her ANCA results were obtained and she was found to be pANCA positive with negative cANCA. Diffuse alveolar hemorrhage was diagnosed based on Chest X ray finding of diffuse infiltrative opacification pattern and HRCT chest showed infiltrates bilaterally more on left side.With this we made diagnosis of AAV, microscopic polyangitis with RPGN and diffuse alveolar hemorrhage. 5th Day of admission: Plasma exchange was initiated for a total of 5 times with approximately 1 time the predicted plasma volume (estimated by the following formula: [0.065×body weight (kg)]×[1-hematocrit]) 11 per session, using freshly frozen plasma as the replacement solution. During this period pulse cyclophosphamide 500mg dose was administered intravenously.

6^{th} Day of admission: Some improvement in lower limb weakness, anuria and chest shadows persisted

After three pulse doses of IV methylprednisolone she was switched to oral prednisone 40mg once a day. After 4 sessions of plasma exchange were performed, her respiratory condition improved, and she was successfully weaned off the ventilator on Day 7. Her urine output improved significantly to 1200ml in 24 hours. Her hemodialysis was stopped.

10th Day of admission: She remained off dialysis for 3 days and now and her serum creatinine level came down to 1.9 mg/dL. She continued to pour good amount of urine. Now, we wanted to do kidney biopsy however patient and her relatives did not consent and could not be convinced. 12th Day of admission: She left hospital on oral prednisone and oral cyclophosphamide.

Table1. Laboratory findings on admission:

Test Descriptions	Value	Test Descriptions	Value
Haemogram		**Thyroid profile**	
White blood cell (/µL)	10,80	TSH (mIU/ml)	4.68
Neutrophil	70	T3(ng/dl)	112
Lymphocyte	24	T4(µg/dl)	17.45
Monocyte (%)	03	**Seroloy**	
Eosinophil (%)	3.6	Antinuclear antibody (dilution)	1:1000
Basophil (%)	0.4	DsDNA	(-)
Hemoglobin (g/d/)	8.3	C3 complement (mg/d/)	98
Hematocrit (%)	30.8	C4 complement (mg/d/)	13.9
Platelet (10^4/ʒ/)	654	cANCA (AU/ml)	(--)
ESR	140	pANCA (AU/ml)	33.0
INR	1.12	Anti-GBM antibody	(–)
Serum Chemistry		**Arterial Blood Gas (room air)**	
Blood Urea (mg/d/)	203	pH	7.23
Creatinine (mg/d/)	7.6	pO_2 (mmHg)	104.0
eGFR(ml/min/1.73 m^2)	5.79	pCO_2 (mmHg)	21
Sodium (mEq/L)	120	$HCO_3^{\acute{i}}$ (mEq/L)	13
Potassium (mEq/L)	5.2	Base excess (mEq/L)	10.6
Chloride (mEq/L)	104	Anion Gap (mEq/L)	7.5
Calcium (mg/d/)	8.2	**Urinalysis**	
Phosphorus (mg/d/)	5.2	Gravity	1.009
C-reactive protein (mg/d/)	5.84	pH	5.5
Uric acid (mg/d)	8.9	Proteinuria	3+
Total Proteins	6.8	UPCR (g/gCr)	3.06
Albumin	3.1	Hematuria	3+
		Red blood cell (/HPF)	6-7

		RBC casts (/HPF)	4-6

Table 2: Laboratory work up:

Sr. No.	Test Description	Test Result
1.	Peripheral smear	Mild anisopoikilocytosis, micrrocytes present with mild hypochromia
2.	Bone Marrow Aspiration	Inadequate erythroid response to anemia and mild plasmacytosis in bone marrow
3.	Serum protein electrophoresis	No abnormality detected
4.	Urine protein electrophoresis	No abnormality detected
5.	Electromyogram/Nerve conduction velocity study	Severe sesorimotor neuropathy asymmetrical, mixed type, involving lower limbs more than upper limbs

Table 3: Investigations flowchart during hospitalization:

Day of Investigation	1 month before admisson	Day 1	Day 3	Day 7	Day 10	Day 12
White blood cell (/µL)	13100	8500		10,400	14,900	
Platelets	284	6.54		5.80	210	
Blood Urea		203	201	61	67	78
Sr Creatinine	0.98	7.6	7.5	3.9	1.9	2
eGFR		5.79				
Sodium		120	119	135	146	138
Potassium		5.7	5.2	4.1	3.4	4

DISCUSSION

We successfully treated an elderly female patient with severe AAV and DAH with immediate institution of haemodialysis, induction regimen of plasma exchange (PE) combined with intravenous methylprednisolone (CS) and cyclophosphamide (CYC)[5]. ANCA associated vasculitis is a multisystem disease with more than 75% of patientswith renal involvement presenting with rapidly progressive glomerulonephritis (RPGN). The etiology and pathogenesis of AAV are multifactorial and individuals are predisposed by genetics, environmental factors including drugs, and responses of the innate and adaptive immune system[6]. Randomized controlled trials in the past 2 decades have advanced the therapy of AAV and transformed AAV from a fatal disease to a chronic disease with relapsing course and concomitant morbidity. The mortality of AAV is very high in cases of critical disease. Strong predictors of increased mortality after admission are mechanical ventilation and admission to the intensive-care unit (ICU)[7]. Our patient although required ICU admission, mechanical ventilation and haemodialysis, she survived and had a remarkable renal recovery also. It is extremely important to institute immediate therapies for severe AAV. Microscopic polyangitis is the most prevalent cause of the P-ANCA pattern. A positive P-ANCA (or MPO) level in the blood confirms the diagnosis and can help differentiate MPA from WG. In 50 percent to 75 percent of patients, the P-ANCA test is positive. The functional impairment of key organs, such as severe renal disease (creatinine>5.7 mg/dL), DAH, or other life-threatening disease, is described as severe disease. In patients who develop lung disease, DAH with pathologic capillaritis is the most common manifestation. Joint, skin, peripheral nervous system, and gastrointestinal involvement are also relatively common.

Hemoptysis, anaemia, widespread lung infiltration, and sudden respiratory failure are all symptoms of DAH, which is an unique clinicopathologic syndrome of pulmonary bleeding originating from the pulmonary microcirculation. The most common cause of DAH is pulmonary capillaritis, which is linked to systemic vasculitis and findings like anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis, anti-GBM disease, systemic lupus erythematosus (SLE), and collagen vascular diseases. It can also occur as a result of other factors, such as the use of certain medicines or transplantation. Congestive heart failure, pneumonia, localised pulmonary bleeding, and other acute manifestations of diffuse parenchymal lung disease were all ruled out.[8-10].

Clinical circumstances suggestive of vasculitis in this case were: 1) DAH, 2) RPRF, 3) pulmonary-renal syndrome, 4) peripheral neuropathy and 5) multisystem disease. [11-12] Although a confident diagnosis can sometimes be reached without a tissue biopsy, a suggestive biopsy is still required for a definitive diagnosis; however in this case we were unable to get a kidney biopsy done as patient was not willing[11]. Because DAH is a medical emergency, a careful and methodical approach to DAH diagnosis is essential for proper therapy, with the goal of establishing the diagnosis and determining the underlying cause. DAH was diagnosed based on particular clinical, laboratory, radiologic, and pathologic characteristics.

Patients with systemic vasculitis had a 75% death rate before immunosuppressive treatment was introduced. Despite significant advances over the previous two decades, individuals with systemic vasculitis who get therapy still have a high death rate. Patients with severe illness may benefit from a combination of CYC, CS, and PE treatment, according to recent

research.[12,13] In patients with severe renal impairment and DAH, adding plasma exchange treatment to the conventional cyclophosphamide plus corticosteroid regimen has been demonstrated to be superior to high-dose, pulsed, intravenous steroids in restoring renal function. In this patient, the disease was controlled with plasma exchange and CYC plus CS and we succeeded in weaning the patient quite early and achieving renal recovery with stoppage of hemodialysis support, good urine output and serum creatinine 2 mg/dl on discharge.[14-18]

CONCLUSION

Our present findings suggest that immediate treatment of severe AAV with DAH with plasma exchanges and intravenous steroids and cyclophosphamide is effective and lifesaving and induced remission of severe AAV in our elderly patient, and also rendered remarkable renal recovery.

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