

Case Report of Rare Entity for Atypical Hemolytic Uremic Syndrome

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Abstract

Background: Atypical Haemolytic Uremic Syndrome (aHUS) is a genetic or acquired disorder of regulatory component of the complement system. It is associated with mutations in genes coding for complement components. The abnormality in components of complement makes it susceptible and predispose to chronic uncontrolled hyperactivation of the alternative complement pathway, which results in endothelial damage and microvascular thrombosis. This case report describes a patient diagnosed with Thrombotic Microangiopathy (TMA) due to factor H autoantibody having haemolytic anemia, thrombocytopenia and acute kidney injury. Patient's anemia and renal parameters improved after treatment with plasma exchange therapy. **Conclusion:** Atypical HUS must be strongly suspected in any patient who presents with nonspecific abdominal or respiratory symptoms along with anemia and thrombocytopenia. As extrarenal involvement is a rare entity of aHUS, the clinician should also keep a high index of suspicion to the possibility of thrombotic microangiopathy manifestation in almost any organ system. In a suspected or diagnosed case of aHUS, the development of new non renal symptoms and signs should prompt clinician for further evaluation to rule out ongoing thrombotic microangiopathy process.

Keywords: Acute Kidney Injury, aHUS, Complement, Dialysis, Plasma Exchange, Thrombotic-Microangiopathy (TMA)

1. Introduction

Atypical Haemolytic Uremic Syndrome (aHUS) are a rare form of thrombotic microangiopathy associated with a genetic or acquired disorder that leads to dysregulation of the alternative complement pathway¹. Factor H heterozygous mutation is a major cause of aHUS. Mutation or polymorphism in proteins are implicated for activation or regulation of alternative complement pathway².

Deletion of CFHR1 and CFHR3 gene is associated with the development of complement factor H autoantibodies

in aHUS, especially those who are at increased risk of genetic predisposition².

More than 80 CFH mutation has been identified of which 40 - 50% are familial and 10 - 20% are sporadic. Coronary and cerebrovascular involvement are seen in 20% cases of haemolytic uremic syndrome³. 10 years' survival rate for patients associated with CFH mutations is 50% whereas those patients associated CFI and C3 mutations or CFH autoantibodies is around 80 to 90%³. Herein, we would like to present a case report of aHUS diagnosed with antibody to complement factor H which is a rare entity for this disorder.

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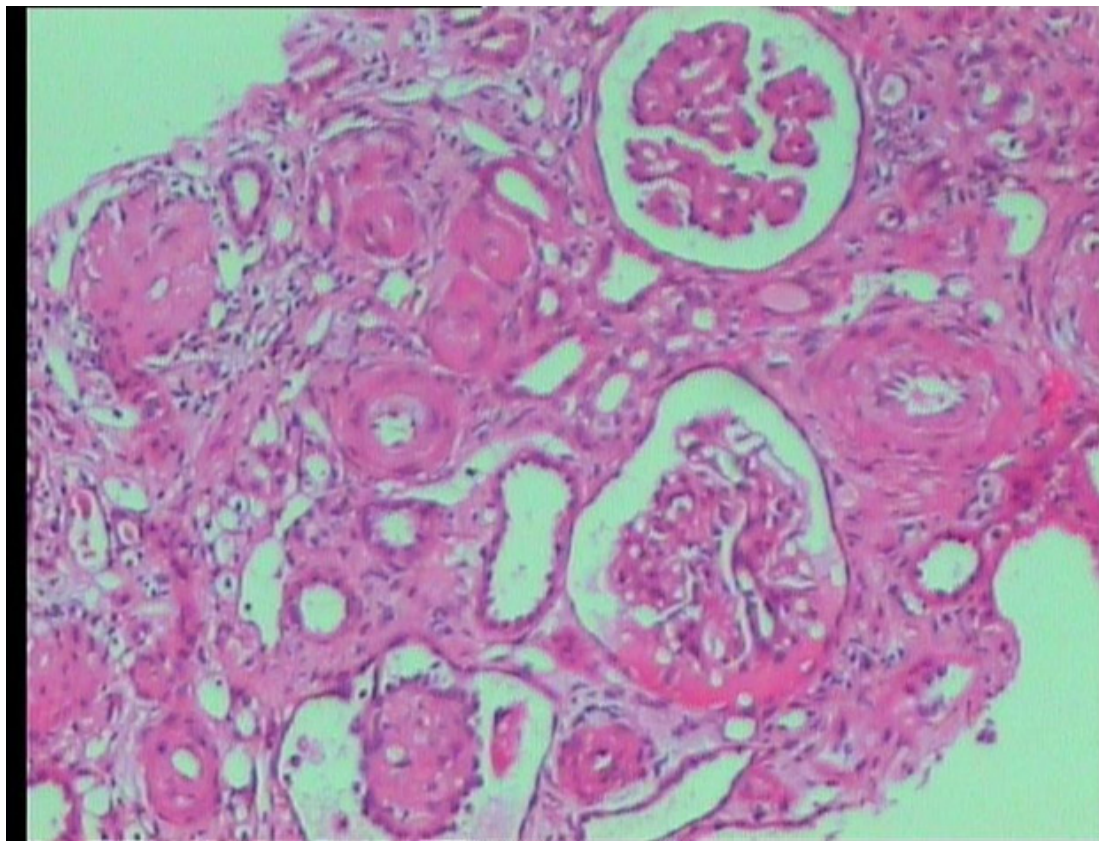
2. Case Report

A 32-year-old male, arc welder by occupation, presented with nausea, blurring of vision, breathlessness on exertion and a decreased urine output. Nausea was not associated with any pain in abdomen, drug abuse, or any recent diarrheal illness.

Patient developed sudden painless blurring of vision in the left eye. On ophthalmologic examination, the patient was found to have bilateral optic neuropathy associated with mild hypertension (BP - 160/90 mm of Hg). Patient developed intravenous methyl prednisolone one gram for three days followed by oral prednisolone 1 mg/kg. Gradually Patient developed breathlessness on exertion. In view of the deteriorating respiratory symptoms, the patient underwent computed tomography scan of chest which revealed a ground glass opacity and reticular

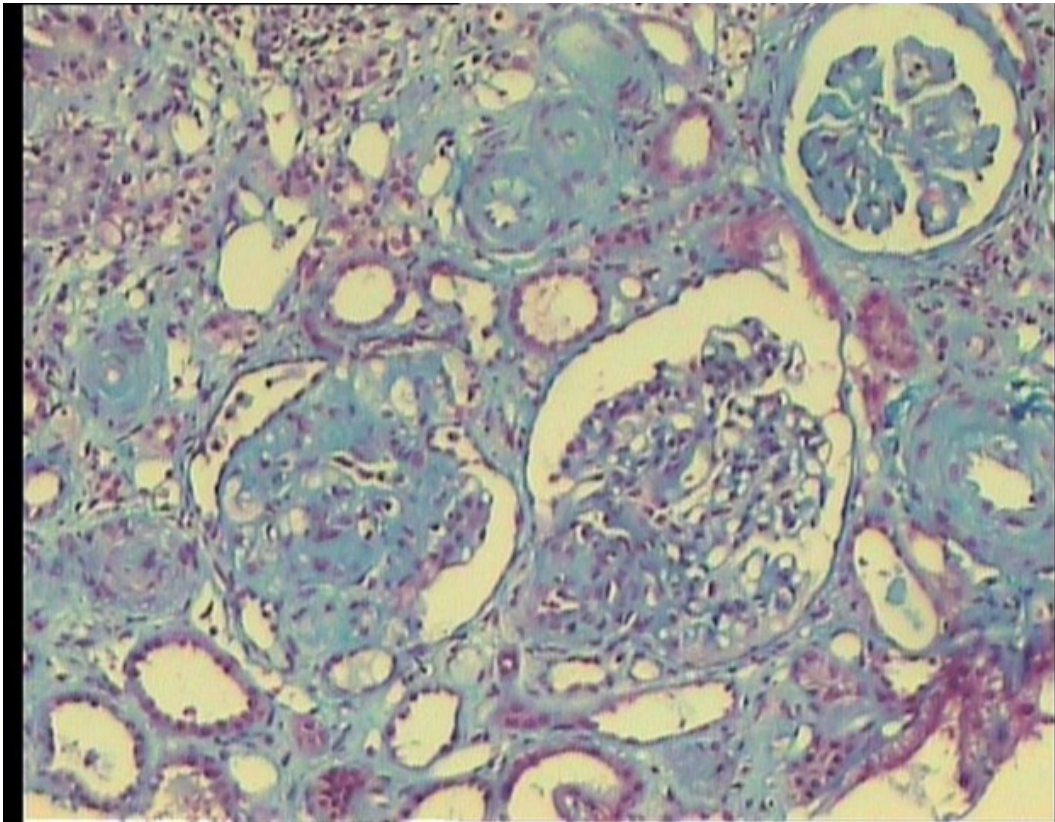
pattern in the lung parenchyma. So patient was suspected of having an arc welder's lung in view of the occupational history or viral pneumonitis. After three days of treatment with intravenous methyl prednisolone, the patient was shifted to oral prednisolone and symptomatic treatment. Over the subsequent 3 to 4 days, the patient's vision improved but respiratory discomfort progressed to orthopnea associated with decreased urine output.

Patient got admitted to another hospital with the above acute symptoms. Clinical data available from discharge summary revealed that the patient had pallor, tachycardia with heart rate of 112/minute and accelerated hypertension with blood pressure - 220/110 mmHg. Patient was tachypnoeic with respiratory rate - 28/minute, low peripheral capillary oxygen saturation (SpO₂) at room air (86 %), and the presence of bilateral coarse crackles on respiratory system examination.



Thrombotic Microangiopathy

Figure 1. Thrombotic Microangiopathy.



Thrombotic Microangiopathy

Figure 2. Thrombotic Microangiopathy.

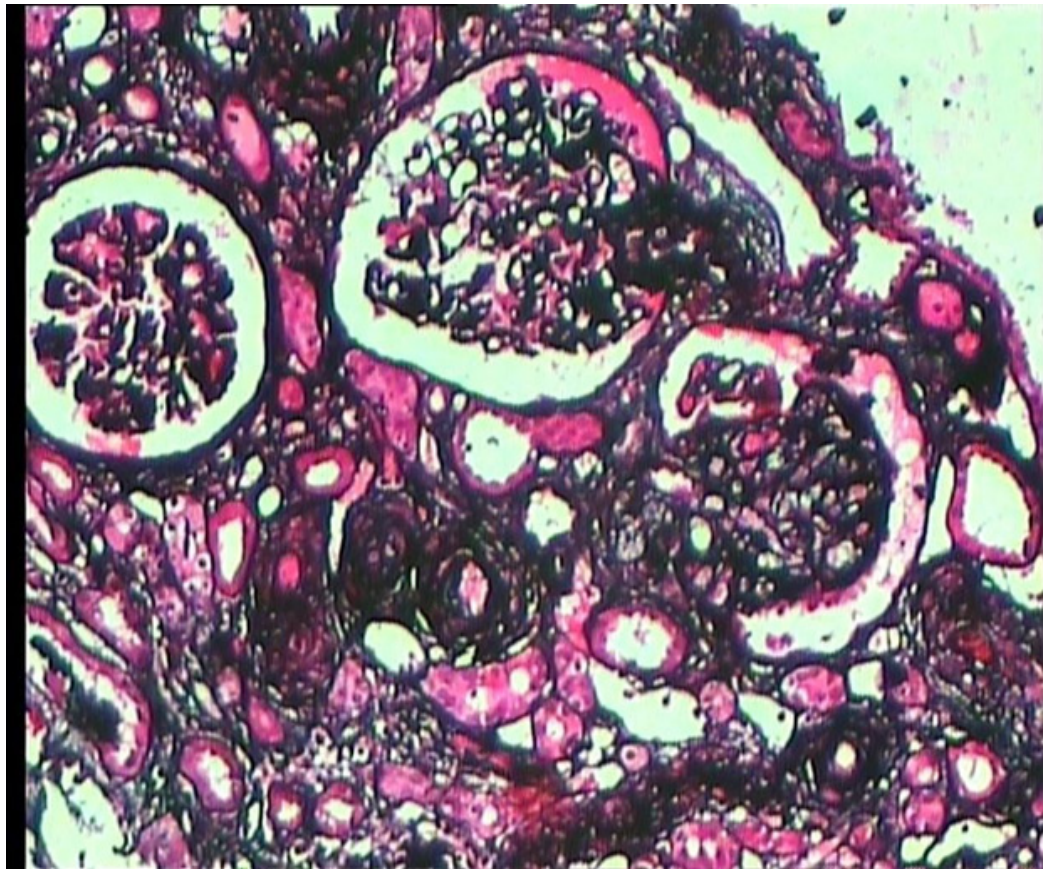
Fundoscopy revealed grade 4 hypertensive retinopathy showing optic disc edema, dot-blot haemorrhages, soft and hard exudates.

Laboratory investigations were suggestive of anemia with Hb-6.8 mg/dl, thrombocytopenia - 99,000/cmm. Serum creatinine - 10 mg/dl, serum urea- 272 mg/dl, serum LDH -1150 u/L, and the peripheral blood smear showed schistocytes. Serum electrolytes, blood glucose, liver function test with prothrombin time and INR were normal. Urine routine microscopy had microscopic hematuria. Electrocardiogram was suggestive of left ventricular hypertrophy pattern; 2 dimensional Echocardiography revealed concentric LVH with ejection fraction of 40%. Chest x-ray was suggestive of pulmonary edema. In view of acute renal failure with pulmonary edema, hemodialysis was initiated with PCV transfusion.

Patient got stabilised with 4 successive hemodialysis and supportive care. Blood pressure control was achieved with oral antihypertensive agents.

Differential diagnosis: 1) Hypertensive heart failure 2) Pulmonary renal syndrome 3) Occupational lung disease 4) Rapidly progressive renal failure with pulmonary edema 5) Pneumonitis with renal failure due to infectious etiology 6) Flash pulmonary edema secondary to renovascular hypertension.

Renal arterial Doppler study was normal thus ruling out renovascular cause of hypertension. C3, C4 normal, and MPO ANCA, PR3 ANCA negative, glomerular basement membrane antibody was also negative. After 4 to 6 days of initial treatment at the above hospital, the patient was subsequently transferred to our tertiary care hospital.



Thrombotic Microangiopathy

Figure 3. Thrombotic Microangiopathy.

On the admission the patient was afebrile, had mild pallor, tachycardia with heart rate of 98/min, and tachypneic with respiratory rate of 24/min. Auscultatory findings was still suggestive of bilateral coarse crackles. So hemodialysis, oral antihypertensives including diuretics, and oral prednisolone was continued.

Strict monitoring of blood pressure, fluid intake and urine output, laboratory parameters were maintained. Follow up thorax imaging study revealed resolving pattern of previous radiological finding. Renal biopsy was done in view of rapidly progressive renal failure.

Positive histopathological finding as seen in Figure 1 showed one out of 11 glomeruli having mesangiolysis with tram tracking appearance. Three glomeruli were globally sclerosed with few ischemic glomerul. Figure 2 shows that under light microscope proximal tubule in normally appearing glomeruli were flattened and

had lost their brush border appearance. Lumen were having necrotic cell debris, RBC cast and denuded lining epithelial cells. In Figure 3, the interstitium showed infiltration by mononuclear cells. Blood vessels showed mucoid intimal hyperplasia with endothelial cell swelling and obliteration of lumina suggestive of accelerated hypertension. Immunofluorescence study including IgG, IgM, IgA, C3, C1q were negative. Impression was acute on chronic phase of thrombotic microangiopathy with hypertensive changes.

Patient completed 8 sessions of hemodialysis without any complication and improved clinically. Patient's vision improved post intravenous methyl prednisolone course as it was prior to this event. Fundus examinations showed regression of previous clinical signs. Further dialysis was withheld and the patient was kept under observations.

On an average intake of 2500 ml to 3000 ml of fluid, the patient had urine output between 2000 ml to 2500 ml. Serum creatinine was in the range of 2 to 3 mg/dl, blood-pressure was controlled with oral hypertensives agent including diuretics.

Following renal biopsy, serum level for ADAMTS13 was done which was found to be normal that is 0.88 IU/mL (normal range- 0.4–1.30 IU/ML - citrated plasma sample). Positive titre for Anti Complement Factor H assay of 207 AU/ML (Normal range: 0–100 AU/mL Kit used: ELISA – VIDITEST) confirmed the diagnosis of Atypical Hemolytic Uremic Syndrome.

We initiated and completed 4 sessions of plasma exchange therapy without any complication. Patient was clinically stable, had improvement in urine output and laboratory parameter. Follow up CT scan of chest revealed complete resolution of ground-glass opacity and reticular pattern. After observation for one week, the patient was discharged on tapering dose of oral prednisolone 40 mg/day and antihypertensive medications. Patient was asked to come for follow up in the medicine opd.

A follow up anti complement factor H assay was done after 8 months. We found a drastic fall in titre as 34.25 AU/ml (Normal range: 0 – 100 AU/mL Kit used: ELISA – VIDITEST). Biochemical parameters also improved in the follow up investigations: Sr. Creatinine = 1.4 mg/dl, eGFR = 70 ml/min/1.73m², WBC=9500/cmm, Hemoglobin = 12.6 g/dl Platelet = 2,20,000/cmm.

3. Discussion and Results

An acute episode of hemolytic uremic syndrome presents as haemolytic anemia, thrombocytopenia, acute renal failure⁴. With plasma exchange and immunosuppressive therapy our patient had a remarkable recovery in clinical as well as laboratory parameters resulting in discontinuation of hemodialysis. Since one year of follow up, the patient is having stable renal function parameters. This is similar to the case study shown by Egerman⁸ and Shemin⁹ who have documented recovery attributed to treatment with plasma exchange therapy. Limitation to our case report study is that the repeat kidney biopsy was not performed as patient had stable renal function parameters in the range of Serum Creatinine = 1 to 2 mg/dl, eGFR = 70 to 60 ml/min/1.73 m².

Plasmapheresis with or without Eculizumab, remains the corner stone of treatment⁶. It provides normal complement levels. Eculizumab is the treatment of choice as it blocks the complement activity by cleavage of complement protein C5 and prevents the generation of inflammatory peptide C5a and cytotoxic membrane attack complex⁵.

When in diagnostic dilemma or due to financial constraints treatment with eculizumab can't be instituted, then immunosuppressive therapy should be initiated. Plasma exchange therapy should be continued until there is improvement in the clinical and laboratory parameters⁷. Our patient in this case report had haemolytic uremic episode for the first time and the event subsided with plasma therapy.

Patients with recurrent episodes of haemolytic uremic syndrome alongwith ESKD and confirmed genetic complement abnormalities can go for liver or combined liver/kidney transplant as a curative option. This is so because the bulk of the circulating complement synthesis is done by the liver. Since aHUS is thrombotic microangiopathy process, other modalities of treatment like antiplatelet agents, heparin, fibrinolytic agents, steroids, IVIg are not effective. Our patient in this case study has received plasma exchange therapy and responded symptomatically and clinically. After observation for one-week patient was discharged on oral steroid 40 mg/day and gradually tapered to 10 mg by 9 months. Patient did strict compliance with antihypertensive and regular follow up.

4. Conclusion

Atypical haemolytic uremic must be strongly suspected in any patients who presents with nonspecific abdominal or respiratory symptoms along with anemia and thrombocytopenia. We found recovery in both clinical and laboratory parameters with plasma exchange and immunosuppressive therapy. Discontinuation of hemodialysis was possible after our patient received above therapy.

We conclude that plasma exchange along with immunosuppressive therapy must be considered as successful treatment modality for atypical haemolytic uremic syndrome. Its beneficial outcome for atypical haemolytic uremic syndrome can be enhanced with early diagnosis and prompt initiation of the above therapy.

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