Coexistence of Anti Neutrophilic Cytoplasmic Antibody (ANCA) Negative Renal Limited Vasculitis and Atypical-Hemolytic Uremic Syndrome (aHUS)

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Small vessel necrotizing vasculitis is divided into two groups; Immune complex mediated and Pauci immune vasculitis. Hemolytic uremic syndrome (HUS) is a rare disease manifested as microangiopathic hemolytic anemia, thrombocytopenia and renal involvement. The coexistence of ANCA negative vasculitis and atypical HUS (aHUS) is rare. We describe a case of a 40 years old lady with rapidly declining kidney function. Renal Biopsy revealed Crescentic necrotizing glomerulonephritis (CGN). She was treated with plasmapheresis alternating with hemodialysis (HD) and immunosuppressive therapy. One month later she developed hemolytic anemia with peripheral schistocytes and thrombocytopenia and diagnosed as aHUS. Same treatment continued and her aHUS resolved spontaneously over one week. However her kidney functions didn't improve and ended up with end stage renal disease (ESRD).

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Case Report

INTRODUCTION

ANCA associated vasculitis is a broad term for a multi-system autoimmune small vessel vasculitis. ANCAs are sensitive and specific markers for ANCA-associated vasculitis. ANCAs are positive in 80 to 90% cases and negative in 10 to 20% of patients.[1] HUS causes thrombotic microangiopathy most commonly affecting the kidney.[2] The pathogenesis of both diseases are linked by dysregulation in alternative complement pathway, genetic association, endothelial dysfunction and infections that trigger other disease process. The simultaneous presence of multiple immune-mediated diseases in a single host is rare.

CASE REPORT

A 40 years female presented with gradual onset of body swelling, dyspnea and cola color urine progressing to anuria for the last 10 days. Autoimmune history was negative. She had Diabetes Mellitus and Hypertension for last ten years with good control. She was diagnosed with Hepatitis C and treated three years ago with sustained viral response. On examination she was tachypneic, hypertensive, pale and edematous. Systemic examination was unremarkable except dextrocardia. Urine analysis showed protein 3+, blood 3+, RBCs 142 to 150/HPF, no cast. At presentation her serum creatinine was 4.1 mg/dL that increased up to 12 mg/dL over 5 days. Trend of hematological and biochemical parameters from admission day till discharge are shown in Table 1. Renal ultrasound revealed bilateral normal size kidneys. Her workup showed low C3 and borderline to low C4 levels while ANA, c-ANCA, p-ANCA, and HBV results were negative. We made a diagnosis of Rapidly Progressive Glomerulonephritis (RPGN) and renal biopsy was performed. HD was initiated

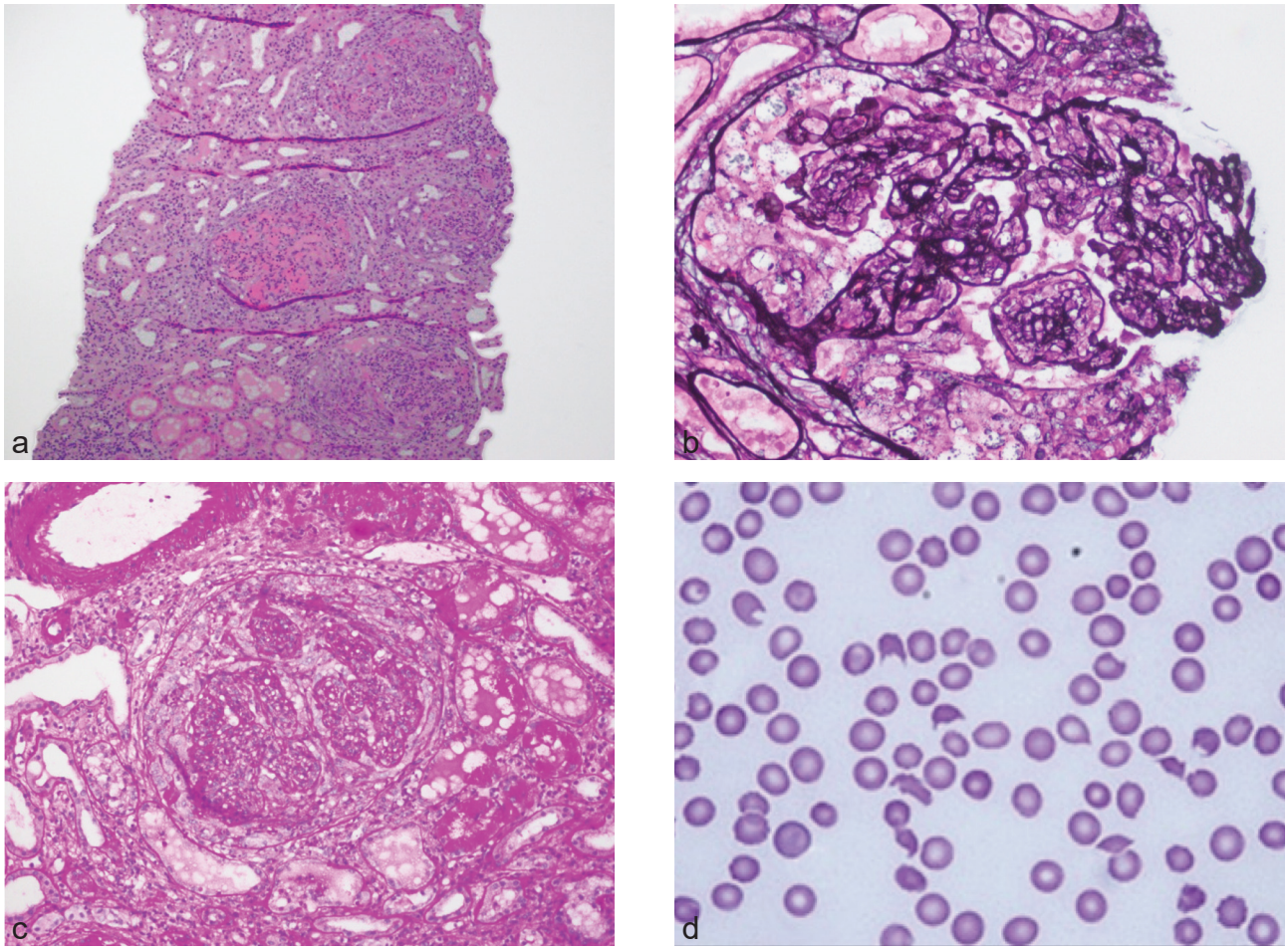
Showing Hematological and Renal Parameters at Day 0, 5, 10, 15, 20, 25, 30, 35, and 40

Parameters	0 Admission Day	5th Day	10th Day	15th Day	20th Day	25th Day	30th Day	35th Day	40th Day
Hemoglobin, gm/dL	7.5	9.4	9.3	9.8	9.5	8.4	8.7	8.5	8.4
Platelet, cells/mm^3	165	142	172	282	223	160	80	62	149
Creatinine, mg/dL	4.1	12.0	9.0	10.0	6.9	6.1	7.5	7.1	6.5
LDH, IU/dL	-	-	-	-	290	300	1600	500	300
Schistocytes	-	-	-	-	-	-	9%	3%	1%
Immunosuppression		Cyclo Phosphamide 1st Dose			Cyclo Phosphamide 2nd Dose			Cyclo Phosphamide 3rd Dose	
HD/ Plasmaphresis		HD Initiated	HD Continued on Alternate Days	HD Continued Alternate Days	Plasmaphresis Initiated	HD and Plasmaphresis on Alternate Days	HD and Plasmaphresis on Alternate Days	HD and Plasmaphresis on Alternate Days	HD and Plasmaphresis on Alternate Days

with immunosuppressive therapy (intravenous methylprednisolone 1 g/d for 3 days followed by oral prednisolone 1 mg/kg/d, and cyclophosphamide 750 mg/m^2). Two units of packed cell transfused with HD. Biopsy report disclosed 20 glomeruli, 18 showing cellular crescents, 1 globally sclerotic, moderate arteriosclerosis, hyalinosis, and focally fibrinoid necrosis [as shown in Figure (a,b,c)]. On the basis of biopsy, diagnosis of ANCA Negative Renal Limited crescentic glomerulonephritis (CGN) was made and plasmapheresis was initiated alternating with HD. One month later she developed thrombocytopenia with 9% schistocytes as shown in Figure (d), with normal profile , raised LDH LDH levels and diagnosis of aHUS was made. Review of medications for possible bone marrow suppression was done. Patient was advised re-biopsy to confirm diagnosis of aHUS but she refused and we couldn't get ADAMTS13 levels, complement factor H and I due to non-availability. Plasmapheresis with HD continued and three doses of cyclophosphamide were also given fortnightly but her kidney functions did not improve. She was discharged on maintenance HD.

DISCUSSION

There is limited data on co-existence of both diseases in a same patient. As far as we know, this is the second case of coexistence of ANCA negative vasculitis and aHUS in the literature, while other case reports show an association between ANCA positive vasculitis with other diseases. One case reported by Stefanids[3] showed coexistence of HUS and C-ANCA associated RPGN due to endothelial dysfunction in which one disease causes insult and triggers the other disease. Another case was reported by Green *et al.*[4] in which there was biopsy proven Pauci immune cresentic GN followed by HUS after two months. While other studies reported co-existence of aHUS with Churg-Strauss Syndrome and Membranoproliferative GN.[5,6] It is therefore suggestive that due to vasculitis, ANCA antibodies from circulation deposit in the glomerular vessels causing damage to vascular endothelium while exposing the hidden antigens and exacerbating another immune process in form of aHUS. In the last couple of years activation of alternate complement pathway in the pathogenesis of ANCA associated vasculitis has been elucidated for neutrophil activation as observed in aHUS as



(a) H & E 10×. Glomeruli showing cellular crescents with focal fibrinoid necrosis. Mild acute tubular injury is also noted in the background. (b) JMS 40×. Glomerulus showing cellular crescent formation, double contouring of basement membranes,and focal endocapillary proliferation. (c) PAS 20×. PAS stain showing cellular circumferential crescents with breech of glomerular basement membrane and focal fibrinoid necrosis. Mild acute tubular injury is also noted in the background. (d). Peripheral Blood smear showing schistocytes.

well.[7] It's now commented that these complement mediated processes may represent a spectrum of diseases which manifest at different times and may have some genetic association.[8] Our patient showed low C3 and borderline to low C4 levels which also support the complement dysregulation. According to literature, when there is coexistence of two diseases, prognosis is very poor.[9] Our patient did not respond to standard therapy and ended up with ESRD. Patients not responding to standard treatment are being managed by humanized anti-C5 monoclonal antibody Ecluzimab.[10] Due to non-availability of this drug in Pakistan, it couldn't be given.

CONCLUSION

ANCA associated vasculitis and aHUS are rare but their coexistence is related by genetic association and complement dysregulation.

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AUTHOR'S CONTRIBUTIONS

MM collected the information regarding the case, contributed to the data acquisition and revised the manuscript. MA analyzed the data, contributed to wrote and revised the manuscript. SA hematological input of the data. MH provided the histopathological analysis of the renal biopsy specimen. SA,IE,FM and All authors read and approved the final manuscript.

CONSENT TO PUBLISH WRITTEN

Informed consent was obtained from the patient

for publication of this case report.

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