Recurrent Hemolytic Uremic Syndrome: A Case Report

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ABSTRACT

Introduction: Hemolytic uremic syndrome (HUS) is a disease caused by *Shiga-like toxin-producing Escherichia coli* most commonly by serotype 0157:H7 characterised as haemolytic anaemia, thrombocytopenia and renal dysfunction.
Case report: Here we present a case of 20 year male patient with prior history of episode of typical haemolytic uremic syndrome (tHUS) and being diagnosed as recurrence of typical haemolytic uremic syndrome.
Conclusion: Patient treated aggressively with plasma exchange and patient improved.

Keywords: Hemolytic Uremic Syndrome, Typical HUS, Atypical HUS, Plasmaphresis

INTRODUCTION

Hemolytic uremic syndrome (HUS) is a disease of nonimmune (Coombs negative) hemolytic anaemia, thrombocytopenia and renal impairment.[1]HUS was first described in 1955 by Gasser et al.[2] HUS is a heterogeneous group of hemolytic disorders and thrombotic microangiopathies that are characterized by prominent endothelial-cell damage.[3] The disease is most commonly triggered by *Shiga-like toxin producing Escherichia coli (STEC)* and manifests with bloody diarrhea.[4] Several serotypes of *E. Coli* are known to cause HUS, the commonest being the serotype 0157:H7. Recurrence of HUS is most commonly observed in patient with atypical HUS (aHUS) and it is less seen in typical HUS (tHUS).[5]

CASE REPORT

A 20 years male patient was admitted with complains of diarrhoea with blood and mucus for last 5 days. Patient was admitted 1 year back with similar complains and was diagnosed as having typical HUS (tHUS). During previous episode of tHUS he was treated symptomatically with hydration. During this second admission, patient's vitals were stable with severe pallor, mild icterus and mild splenomegaly. We suspected a recurrence of tHUS on the basis of his diarrhoea, laboratory reports and his past history of similar symptoms. There was no history of fever, burning micturition, seizure, unconsciouness and vomiting. The Laboratory Investigation at the time of admission is shown in table 1.

Patient was treated symptomatically with hydration, 5 cycles of plasma exchange with FFP and 4 units of packed cell transfusion to correct his anaemia. He was subsequently started on tablet Prednisolone 1mg/kg and tapered over 15 days. Patient was discharged after 15 days of treatment and was asymptomatic on follow up with normal laboratory findings. (Table 2 and 3)

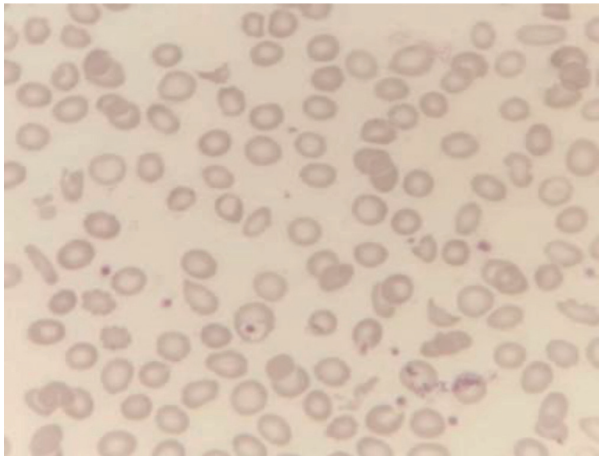

Figure-1: Peripheral Smear showing schistocytes

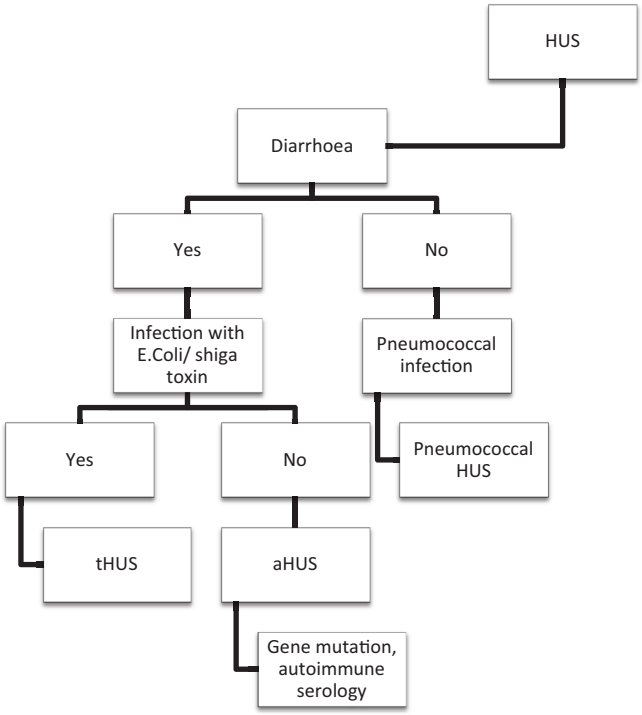

Figure-2: Algorithm for evaluation of HUS[6]

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Laboratory parameter	Value
Haemoglobin	5.4 g/dl
Platelet count	30,000/ul
Blood Urea	160 mg/dl
Serum Creatinine	5.7 mg/dl
Indirect bilirubin	6.2 mg/dl
LDH	4330 IU/L
Urine examination	RBCs 15-18/hpf
Prothrombin time INR	1.3
Coomb's test	Negative
Urine for haemoglobinuria	Present
Peripheral smear (Figure 1)	Normocytic normochomic RBCs with Schistocytes
Retic count	2 %
Stool culture	Growth of *E. Coli*
Serum Sodium	128 mEq/L
Serum Potassium	3.6 mEq/L
C3 complement	57.90 (90-180)
ANA	9.0 (<20)

Table-1: Laboratory Investigation at the time of admission

Day	1	2	3	4	5	6	7	8	9
Plasma exchange cycle		1	2	3	4	5			
Blood Urea	160	198	163	158	134	84	76	42	36
Serum Creatinine	5.7	6.2	3.2	2.4	2.4	1.8	1.6	1.1	0.9
LDH	4330	4300	2110	1500	780	550	413	225	218
Output	1150	1000	1600	1800	2200	2350	2350	2600	2870

Table-2: Laboratory parameters during hospitalisation

Laboratory parameter	Value
Haemoglobin	12.1 g/dl
Blood Urea	36 mg/dl
Serum Creatinine	1.0 mg/dl
Platelet count	195000/ul
Indirect bilirubin	0.8 mg/dl
LDH	218 IU/L
Urine examination	Normal

Table-3: Laboratory reports at the time of discharge

1. Microangiopathic haemolytic anaemia (coomb's negative)
2. Thrombocytopenia
3. Acute kidney injury

Table-4: Criteria for diagnosis of HUS[1]

Criteria	HUS	TTP
Age	Infancy to adulthood	Most commonly adults
Clinical presentation	Bloody diarrhoea Microangiopathic haemolytic anaemia Acute kidney injury Thrombocytopenia	Fever Neurological manifestations Severe thrombocytopenia Microangiopathic haemolytic anaemia Less severe renal dysfunction
Diagnosis	Stool culture shows *E.coli/shiga toxin* C3 levels normal or low ADAMTS 13 activity normal	ADAMTS 13 activity low
Treatment	Symptomatic with hydration Plasma exchange or plasma infusion in recurrence and aHUS Anti complement therapy with eculizumab in aHUS	Plasma phresis ADAMTS 13 guided rituximab

Table-5: Comparison of HUS and TTP[10]

DISCUSSION

Thrombotic microangiopathies (TMA) are microvascular occlusive disorders characterized by platelet aggregation and mechanical damage to erythrocytes.[6] In HUS most common organ involved is the kidney, whereas in thrombotic thrombocytopenic purpura (TTP) there are predominant manifestations of the nervous system.[7] In tHUS, the commonest is diarrhea causing *E. Coli* infection.[8] Sometimes it is also caused by enteric infection with *shiga toxin producing shigella dysenteriae*. *E coli* adhere to and efface intestinal cells and release *Shiga like toxin* which binds to globotriaosyl ceramide (GB3) membrane receptors presented on endothelial cells of kidney and disrupts protein synthesis which causes endothelial cell death and damage, induces inflammatory and procoagulant cascades that promote microvascular thrombosis.[5,9] In aHUS there are various etiology to develop TMA and renal dysfunction. In pneumococcal HUS, renal endothelial cells, erythrocytes and platelets have a structure on their surface called Thomsen-Friedenreich antigen (TAg) which is normally obscured by neuraminic acid. Pneumococci containing neuraminidase enzyme able to cleave this neuraminic acid from the cell surface thus exposing the TAg to pre-formed anti-TAg IgM.This leads to antigen-antibody binding, activation of an immune cascade with resultant glomerular endothelial cell damage, haemolytic anaemia, platelet aggregation and consumption and a fall in GFR.[10] In patients with complement abnormalities there is presence of complement gene mutations, abnormalities in the Factor H (FH) gene, membrane co-factor protein (MCP) gene and membrane co-factor protein (MCP) gene seen.[2] Acquired forms of ADAMTS13 deficiency is more commonly seen in adults which present in TTP.[8] Abnormalities in intracellular vitamin B12 metabolism, HIV, systemic lupus erythematosus, antiphospholipidsyndrome, malignancies, radiation and certain drugs (e.g. cyclosporine, quinine, oralcontraceptives etc.) are also causes HUS.[1] (Table 4)

The commonest clinical presentation of HUS is with bloody diarrhea.[6] Peripheral blood smears shows fragmented RBCs (schistocytes, burr cells and helmet cells). Laboratory parameters reveals thrombocytopenia, high levels of reticulocyte and LDH, unconjugated hyperbilirubinemia and low serum haptoglobin levels. Urinalysis reveals hemoglobinuria, hematuria and proteinuria.[4] In patients with diarrhea, the presence of pathogenic *E coli* or *Shigella* is seen in stool culture and further serotyping by agglutination or enzyme immunoassay.[6] (Figure 2) The C3 levels may be transiently low in tHUS and persistently low in aHUS due to complement factor deficiency. Autoimmune serology (ANA, anti-dsDNA, antiphospholipid antibodies) and HIV screening may be indicated. Renal biopsy may be indicated in partial forms where the diagnosis is in doubt. In tHUS, fibrin thrombi are found in glomerular capillaries and in aHUS, the thrombi are made up of a combination of fibrin, platelet and VWF clumps that involve larger renal and interlobular arterioles.[1] Patient in present case report had bloody diarrhoea with evidence of haemolysis, renal dysfunction and stool culture showed *E. Coli*.

Supportive care with particular attention to fluid replacement and renal support is the mainstay of treatment for patients with tHUS.[10] Evidence for the addition of plasma-based therapy to supportive care for the treatment for tHUS is limited and mostly used to treat recurrence of tHUS. It is recommended not to use antibiotics to treat *Shiga toxin-producing Escherichia coli (STEC)* infection because of either no benefit or potential increase in the risk of developing HUS.[10] (Table 5) Several other treatments for tHUS including oral administration of Shiga toxin-binding agents, corticosteroids, anti-platelet agents and heparin have been suggested but have not proven beneficial. In our case as we diagnosed recurrence of tHUS we went for plasma phresis. some data suggest that oral steroids are not able to modify haematological clinical parameters during the acute phase of HUS even though they do seem to be associated with a more rapid decline in serum creatinine levels.[6,7] In our case we treated with corticosteroids and plasma exchange. Plasma exchange (PE) until recently has been considered the most effective treatment which removes functionally defective proteins and overactive proteins. The effective use of eculizumab in aHUS was first described in 2009 which helps in controlling haemolysis, improving renal function and allowing the withdrawal of plasma therapy.[9]

Commereuc *et al* reported a case of recurrent HUS with consumption of raw milk from cow. They treated patient symptomatically in first episode and with plasma phresis in second episode.[9] In a case reported by Fabiel Gerardo *et al* suggests that delayed plasma exchange in HUS results in neurological and renal complications which requires long term hospital stay to recover.[6] In our case the first episode had resolved spontaneously with symptomatic treatment. The second episode was aggressively treated with plasma phresis, hydration, correction of anaemia and steroid with better results and early recovery.

CONCLUSION

Most commonly, Hemolytic Uremic Syndrome is due to *Shiga toxin-producing Escherichia coli* infection. In most the cases it is self-limiting and will resolve completely. Although the role of plasma exchange in tHUS secondary to STEC infection remains controversial,it has been suggested that plasma exchange may improve the outcome. The early treatment with plasma exchange with FFP in patient with recurrence of typical haemolytic uremic syndrome gives better outcome. There is still scope for more clinical trials to formulate treatment for recurrence of tHUS.

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