Case Report H**aemolytic Uraemic Syndrome: An Unusual Cause of Jaundice**

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Abstract

Introduction

Haemolytic uremic syndrome (HUS) is a disease characterised by microangiopathic haemolytic anaemia, thrombocytopenia and renal impairment. It can be either typical HUS- caused by shiga toxin producing enterohemorrhagic *Escherichia coli* or atypical HUS- caused by mutation in the gene for complement proteins (1). HUS should be considered in patients presenting with jaundice to the emergency room in the setting of the above mentioned triad.

Case Report

This case report is about a 41 year old lady who presented with jaundice, thrombocytopenia, anemia and renal failure. In the course of investigating the cause of her symptoms, a diagnosis of HUS was made and she was commenced on therapeutic plasma exchange and hemodialysis.

Conclusion

The main lesson is to raise awareness of HUS as a possible cause of jaundice among physicians, especially those in the emergency care.

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Case report

A 41-year-old woman presented at the medical emergency with an eleven-day history of jaundice, malaise and headaches. She was also found to have nausea, anorexia, vomiting, oliguria and dark coloured urine. She had no fever, abdominal pains, diarrhea or pruritus. There were no symptoms referable to the respiratory or cardiovascular systems. Her past medical history was significant for Raynaud syndrome for 20 years, hypertension for 1 year and vascular headaches for 6 months. She did not have a past history of jaundice, blood transfusion, multiple sexual partners and use of illicit drugs or anabolic steroids. She had been taking amlodipine 5mg daily for hypertension, Ibuprofen and paracetamol for chronic headaches. She had no family history of liver disease and had a sister who was being treated for systemic lupus erythematosus (SLE). Examination revealed a young woman who was acutely ill looking, icteric, pale, afebrile, peri-orbital edema, no peripheral lymphadenopathy. She had tachycardia of 105 beats per min, elevated B.P. of 180/110mmHg, normal heart sounds and a systolic murmur. Other systemic examinations were unremarkable.

Table 1: Temporal profile of biochemical and hematological investigations

Biochemical parameter	Date of follow-up		
	Reference Range	03/06/2009	04/06/2009
Haematocrit (%)	36-46	36	32
White cell count($x10^3/\mu l$)	3.5-11	17.2	11
Platelet count (x $10^3/\mu l$)	150-350	23	15
Proteinuria	Neg	4+	
Glycosuria	Neg	1+	
Erythrocyturia	Neg	3+	
Haptoglobulin µmol/l	0.35-1.9	<0.07	<0.07
ASO IU/ml	>125		13.7
Rheumatoid factor IU/ml	<20		8.2
Sodium (mmol/l)	135-145	136	
Potassium (mmol/l)	3.4-4.8	3.2	
Calcium (mmol/l)	2.0-2.4	2.28	
Chloride (mmol/l)	95-110	100	
Creatinine (µmol/l)	53-126	176	266
Urea (mmol/l)	1.3-7.5	16.5	24.2
Bilirubin (µmol/l)	0-18	95	68.5
Bilirubin-direct (µmol/l)	0-7.2	18.2	
LDH (µmol/l)	0.4-1.7	31.1	40.1
AST (U/l)	9-32	1.69	
ALT (U/l)	7-30	0.5	
Albumin (g/l)	35-50		32.9
CRP (mg/l)	0-5	76.9	130.5
Myoglobulin (ng/ml)	1-66		159
Anti HAV IgM		Neg	
HBsAg		Neg	
Anti HCV		Neg	
Alpha 1 globulin (g/l)	2.5-5		5.7
Alpha 2 globulin (g/l)	7-13		13.8
Beta globulin (g/l)	8-14		12.4
Gamma globulin (g/l)	12-22		13
Fragmented red cells			Positive

The following differential diagnoses were considered: Hemolytic uremic syndrome (HUS); malignant hypertension and viral hepatitis. However, with the above investigations: [A] Evidence of hemolytic anemia as shown by presence of fragmented red cell in the blood film report; elevated LDH of 31 μmol/l and reduced haptoglobulins of <0.07 μmol/l, [B] Low platelets of 23 x 10^3 /μl, [C] Renal impairment: elevated serum urea of 24.2 mmol/l, elevated serum creatinine of 266 μmol/l, proteinuria 4+ and red cell casts; a definitive diagnosis of HUS was made. These are shown in table 1 above.

She was commenced on: I.V. prednisolone 100mg daily, pantoprazole 40mg daily, amlodipine 5mg daily, Urapidil 60mg tds and calciferol 400 iu daily. Due to worsening symptoms of uremia, she was commenced on haemodialysis (HD). Initial HD was performed through an internal jugular access route. This was later converted to a tunnelled catheter and an artero-venous fistula was created for long term hemodialysis. She also commenced therapeutic plasma exchange (TPE). Plasma exchange was performed using fresh frozen plasma (FFP), 20 sessions were performed over a period of one month. In the course of TPE, her platelet count improved remarkably to >100 x10^3 /μl and this was stopped. She thereafter continued thrice weekly in center hemodialysis on account of chronic kidney disease secondary to HUS.

Discussion

Haemolytic uraemic syndrome (HUS) is a disease of nonimmune (Coombs negative) hemolytic anemia, low platelet count, and renal impairment.[1] Anaemia is severe and microangiopathic in nature, with fragmented red blood cells (schistocytes) in the peripheral smear, high serum lactate dehydrogenase (LDH), circulating free haemoglobin, and reticulocytes. Platelet count is 60 x10^3 /μl in most cases.[1]

The majority of HUS episodes are triggered by *Escherichia coli* 0157:H7 infection. However, a minority of cases are not associated with infection; this form, termed atypical HUS (aHUS), has the poorest long-term prognosis.[2]

The major cause of HUS in childhood is infection with verocytotoxin (shiga-like toxin)-producing bacteria, usually enterohemorrhagic *Escherichia coli* (VTEC/STEC)[3] and in some tropical regions *Shigella dysenteriae* type I.[4] The disease begins after an incubation of 4–7 days with abrupt onset of diarrhea, usually bloody, with abdominal pain. Microangiopathic hemolytic anemia, thrombocytopenia and acute oliguric renal failure occur 2–10 days later. The diagnosis of VTEC infection is made on stool culture, identification of toxin in the stools, or by serological response to the relevant O-serotype. Verotoxin itself is implicated in

the pathogenesis, both from the epidemiology and from laboratory models. A pro-thrombotic state evolves prior to the acute renal failure[5] and the specific pathological finding is glomerular thrombosis.[6, 7]

Atypical HUS on the other hand accounts for 5-10% of all HUS cases.[8] It may manifest at all ages but is more frequent in adults. The onset may be preceded by the nephrotic syndrome and a diarrhea prodrome is rarely observed. Atypical HUS can occur sporadically or in families.[8] A wide variety of triggers for atypical HUS have been identified, including various non-enteric infections, viruses, drugs (cyclosporine, tacrolimus, OKT3, IFN, quinidine, ticlopidine and clopidogrel), malignancies, transplantation, pregnancy, and other underlying medical conditions like: scleroderma, antiphospholipid syndrome and lupus.[8] Familial forms account for fewer than 3% of all cases of HUS. Both autosomal dominant and autosomal recessive forms of inheritance have been noted.[9] Mutations in the genes for complement factor H (FH), factor I (FI), and membrane co-factor protein (MCP), also known as CD46, are associated with HUS.[7] These complement factors regulate the complement pathways and are therefore responsible for the activation of C3 which is degraded during complement activation and found to be usually low in these patients.

Treatment for HUS include: antibiotics and supportive therapy; for those who develop chronic kidney disease, angiotensin converting enzyme inhibitors therapy, dialysis and kidney transplantation have shown good outcome. The rate of recurrence of HUS in the recipient is low, about 10%.[8] For atypical HUS, treatment is slightly different, as the patients require plasma exchanges and there is high rate of HUS recurrence in the grafted kidney. On this account, simultaneous kidney and liver transplant is preferred, as the liver is the site of synthesis of the complement factors implicated in the aetiology of atypical HUS.[8] The use of eculizumab, a recombinant monoclonal antibody, inhibits terminal complement activation at the C5 protein has been reported to have restored kidney function in patients previously on dialysis and plasma exchange.

A study of the aetiology of acute kidney injury in children in Ile-Ife by Olowu *et al*[11] revealed that HUS accounted for 5.5%. Another study on acute diarrhoea in adults in Southwest Nigeria by Okeke *et al*[12] showed that enterohemorrhagic *E.coli* remains one of the three most common organisms implicated in bloody diarrhoea. These two studies underscore the fact that though uncommon as a cause of renal impairment, a high index of suspicion must be maintained by emergency and family physicians in general.

Differential diagnoses considered in this case were malignant hypertension and viral hepatitis. The former was considered in view of the elevated blood pressure (180/110mmHg)

and the presence of fragmented red blood cells, but it could not account for many abnormalities in her serum biochemistry. The latter was excluded based on the negative serology for hepatitis (and the anomalies in the serum biochemistry).

A vital lesson in this case is that jaundice can present as a component of HUS, a condition that is not usually included in the differential diagnoses of jaundice presenting in the emergency room. There should be a high index of suspicion on the part of our emergency room physicians to detect these patients early and institute appropriate management.

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