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CASE REPORT

Atypical haemolytic uraemic syndrome- A case report

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ABSTRACT

We are presenting an 11 years old girl with Atypical HUS (haemolytic uraemic syndrome). The patient presented to us as a case of acute gastritis with h/o haematuria since 3 days. On investigations, the child was found to have anaemia-Hb-6.5g% WBCcounts-8600/mm^3, platelets-2.24lac/mm^3. Urea 93 mg/dl, Creatinine 2.7mg/dl, K+ 2.7mEq/L, Na+ 125mEq/L Peripheral smear showed moderate microcytic anaemia with Microspherocytes, Helmet cells, Schistocytes, Anisocytosis, suggestive of haemolytic anaemia. Child was found to have sky rising reticulocyte count of 28%, hence, she was suspected to be a case of atypical HUS. Factor H antibody levels were sent, which came out to be positive (5021 AU/ml), confirming the diagnosis of atypical HUS.

Keywords: HUS, Atypical HUS, Factor H, Complement pathway

1. INTRODUCTION

Hemolytic uremic syndrome (HUS) is a classic disease of nephrology, initially described as fatal renal cortical necrosis in children[1]. It is defined a triad of Microangiopathic haemolytic anaemia (MAHA), thrombocytopenia, acute renal failure. It is broadly divided into 4 types, infection induced, mostly post dysentery(typical) or post pnemococcal, remaining types fall under atypical HUS, i.e genetic causes(complement dysregulation), medication induced ,and secondary to other diseases .e.g. SLE. The most common form of HUS is caused by toxin producing Escherichia coli that cause prodromal acute enteritis and is commonly termed diarrhoea associated HUS[2]. The major toxins that cause haemolytic uremic syndrome, Shiga toxin 1 (Stx1) and Shiga toxin 2 (Stx2). These toxins bind to globotriaosylceramide (Gb3), a glycolipid receptor molecule on the surface of endothelial cells in the gut, kidney, and, occasionally, other organs. Damaged endothelial cells of the glomerular capillaries release vasoactive and platelet-aggregating substances. Swelling and microthrombi formation within the glomerular capillaries produce a localized intravascular coagulopathy. The glomerular filtration rate is reduced, and renal insufficiency ensues. Erythrocytes

are damaged and fragmented as they traverse the narrowed glomerular capillaries. This leads to the characteristic microangiopathic hemolytic anemia. Children with epidemic diarrhea-associated HUS are not treated with plasma exchange, and nearly all recover from acute episodes[3].However, in case of atypical HUS, the pathogenesis is different. Atypical hemolytic uremic syndrome (aHUS) is now well recognized to be a disease characterized by excessive complement activation in the microvasculature. In both the familial and sporadic forms, inherited and acquired abnormalities affecting components of the alternative complement pathway are found in ~ 60% of patients. These include mutations in the genes encoding both complement regulators (factor H, factor I, membrane cofactor protein, and thrombomodulin) and activators (factors B and C3) and autoantibodies against factor H. Multiple hits are necessary for the disease to manifest, including a trigger, mutations, and at-risk haplotypes in complement genes. The prognosis for aHUS is poor, with most patients developing end-stage renal failure. Renal transplantation in most patients also has a poor prognosis, with frequent loss of the allograft to recurrent disease.

2. CASE REPORT

A 11 yr old girl came to the hospital with chief complaints of pain abdomen and vomiting since 1 week. There was a history of passage of cola coloured urine since 3 days and pain abdomen with vomiting ,pain was sudden in onset, localized to upper abdomen, dull aching, intermittent, no association with food intake. Urine was cola coloured urine since last 3 days. There was no h/o burning sensation in micturition but urine was frothy. H/o mild fever one spike 3 days back. There was h/o sore throat 15-20 days back.Child also had h/o wt loss, apetite loss.There was h/o exertional breathlessness since one month (NYHA GradeII). There was no previous h/o haematuria/blood transfusion/headache. There was no h/o gastroenteritis/dysentery. On examination,she had severe pallor, mild icterus, chest was clear,no adventitious sounds, heart sounds S1,S2 heard with a soft haemic murmur. Per abdomen, liver was palpable 2cm below rt. subcostal margin. Her first lab reports were-Hb-6.5g%, TLC 8600/mm^3, Platelets 2.24/mm^3, Urea 93 mg/dl, Creatinine 2.7mg/dl, K+2.7mEq/L, Na+125mEq/L, bilirubin-3.6mg/dl, SGOT 80U/L, SGPT 75U/L, cholesterol 238mg/dl. Urine R/M-Proteins+, Pus cells 3-4/hpf, RBC: 40-50/hpf, Ep cells 1-2/hpf, Granular casts+, Bacteria+, Blood c/s, urine c/s were sent. We were suspecting PSGN initially but one thing against this was the icterus. Urgent ultrasonography of the abdomen was done which revealed bilateral raised echogenicity and loss of corticomedullary differentiation. There was no evidence of renal vein thrombosis. Gall bladder was distended with sludge within. We did serum complement levels, C3-0.97(0.90-1.8g/L), C4-0.32(0.10-0.40g/L), which came out to be within normal range. Viral markers for HAV, HCV, HepB were negative. Peripheral smear showed microcytic hypochromic anaemia with anisopoikilocytosis, microspherocytes, helmet cells, schistocytes indicating haemolytic anemia. We did reticulocyte count of the child which came out to be as high as 28%.LDH was3066.Direct coomb's test was negative. Hence, ATYPICAL HUS was suspected since there was no h/o gastroenteritis. She was worked up for diseases secondarily causing HUS; ANA, anti dsDNA- negative. Anti Factor H antibody was found out to be positive:5021 AU/ml (Arbitrary units/ml), which confirmed the diagnosis of ATYPICAL HUS.

Child was started on i.v antibiotics i.e. ceftriaxone to treat underlying U.T.I, later antibiotics stepped upto piperacillin tazobactam in renal dosage (30% reduction) in view of persistence of the pus cells. Child had hypokalemia since day1, which was corrected gradually by K+ supplementation through iv fluids, initially 1% of the iv fuild, later 1.5%, then upto 2% of iv fuild was given.ECG revealed no hypokalemic changes. Once K+levels were normalized, i.v fluids were omitted and child was put on oral K+ supplements. Blood pressure, urine output, urine albumin and abdominal girth were monitored. Child had normal blood pressure for her age initially. Urine albumin was 3+. Towards the end of the first week of admission, child had developed periorbital oedema, and her Hb had dropped down so low i.e. 6.1g%, that she had to be transfused with PCV twice. Despite being on antibiotics, child had 12-14 pus cells/hpf, hence, cefoperazone sulbactam was added. Child maintained urine output>1.5cc/kg/hr. In the second week, however, the child started deteriorating, creatinine levels were around 1.5mg/dl constantly and urea level around 60mg/dl. We did 3 consecutive days urine culture- no organisms were isolated. No organisms were isolated even on blood culture. However, the child showed improvement in the U.T.I. RBCs in urine had fallen from 40-50 to 1-2/hpf. But the child again relapsed, on day 10 of admission, her urine showing RBC-20-30/hpf, bacteria+. By now, the child had become hypertensive, she was started on nifedipine @0.3mg/kg/day, still her B.P was >95th percentile hence, later nifedipine increased to 0.4mg/kg/day. Her urine output also started showing a fall averaging between0.5-1cc/kg/hr. No evidence of renal vein thrombosis seen on urgent ultrasound abdomen. Child's urine showed relapsing remitting pattern of passage of RBC, suggesting ongoing renal injury. But, platelet counts never went below 1 lac/mm^3. However, her Hb dropped down to 4.4, and she had to be transfused with 2 more units of PCV. Nephrology opinion taken and child was transferred to their side for further management. There she was given dexamethasone pulse dosing for 3 days @ 5mg/kg/d on alternate days. On the 3rd day of receiving steroid, child had developed cellulitis of bilateral thigh, abdomen and chest. Child was started on i.v ampicillin cloxacillin, still she did not respond, hence, antibiotics stepped up to piperacillin tazobactam and linezolid. But child had progressed to septic shock. The child went into refractory shock and could not be saved. Plasmapheresis could not be done as the child could not survive till that time.

Her serial renal function tests-

	6/4/15	7/4/15	8/4/15	9/4/15	10/4/15
Urea (mg/dl)	93	72	60	55	64
Creatinine(mg/dl)	2.7	2.2	2.8	1.9	2.0
Na+(Meq/L)	125	130	134	131	137
K+(Meq/L)	2.6	2.0	2.9	3.7	3.4

Shruti et al.
Atypical haemolytic uraemic syndrome- A case report,
Medical Science, 2015, 18(72), 11-15,
www.discovery.org.in

	11/4/15	13/4/15	14/4/15	16/4/15	18/4/15
urea(mg/dl)	58	50	62	64	60
creatinine(mg/dl)	1.8	1.5	1.5	1.6	1.5
Na++(Meq/L)	134	134	138	136	133
K+(Meq/L)	2.4	3.5	3.4	2.9	3.0

	21/4/15	24/4/15	25/4/15	26/4/15
urea(mg/dl)	69	65	76	65
Creatinine(mg/dl)	1.8	1.7	1.8	1.6
Na+ (Meq/L)	132	130	133	133
K+ (Meq/L)	3.3	3.1	3.1	2.9

Her serial cbc are as follows-

	6/4/15	7/4/15	8/4/15	10/4/15	13/4/15	15/4/15	16/4/15	20/4/15	22/4/15
Hb(g%)	6.5	7	6.1	9.7	6.8	4.4	7.9	9.2	7.2
TLC(/mm^3)	8600	8000	3000	5300	15000	3900	4000	5400	4000
Platelets (Lakh/mm^3)	2.24	2.62	2.05	1.98	1.45	1.06	1.53	1.33	1.34
N%	75	70	60	65	80	60	50	75	65
L%	20	25	35	31	25	35	45	20	30
M%	3	2	3	2	2	3	3	3	2
E%	2	3	2	2	3	2	2	2	3

Her serial urine r/m-

Urine	4/4/15	6/4/15	9/4/15	13/4/15	17/4/15	20/4/15	22/4/15	24/4/15	25/4/15
Albumin	+	+++	+++	++	+++	++++	+++	trace	trace
R.B.C (/hpf)	40-50	8-10	5-6	1-2	50-60	55-60	8-10	nil	2-3
Epithelial cells(/hpf)	1-2	5-6	3-4	3-4	1-2	1-2	3-4	1-2	1-2
Pus cells(/hpf)	3-4	90-100	12-14	nad	3-4	20-30	6-8	1-2	1-2
Parasites crystals	-								
others	Granular casts+					Sugar+			
	Bacteria+				Bacteria+				

Shruti et al.
Atypical haemolytic uraemic syndrome- A case report,
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www.discovery.org.in

3. DISCUSSION

Atypical hemolytic-uremic syndrome is a rare disease that primarily affects kidney function. This condition, which can occur at any age, causes abnormal blood clots (thrombi) to form in small blood vessels in the kidneys. These clots can cause serious medical problems if they restrict or block blood flow. Atypical hemolytic-uremic syndrome is characterized by three major features related to abnormal clotting: hemolytic anemia, thrombocytopenia, and kidney failure. While Stx HUS typically is preceded by a gastroenteritis and is associated with infection by Shiga toxin producing-E.coli, there is substantial evidence that aHUS is a genetic disorder. Atypical hemolytic uremic syndrome may become a chronic condition, and patients with aHUS may experience repeated attacks of the disorder. When children with Stx HUS recover from the life-threatening initial episode, they are likely to respond well to supportive treatment and to make a good recovery. The most common form of HUS is caused by toxin producing Escherichia coli.In the UK and Ireland, the two British Paediatric Surveillance Unit prospective surveys (1985-1988 and 1997-2001) of HUS in children under 16 years reported a strong association in the incidence of HUS and age, with children under five years of age being most commonly affected[4]. Atypical HUS represents 5 -10% of HUS in children, but the majority of HUS in adults[5]. In this case,child was aged 11 yrs, with no antecedent h/o gastroenteritis, hence Atypical HUS was suspected. Children with aHUS are much more likely to develop chronic serious complications such as kidney failure and severe high blood pressure. Atypical HUS most of the times has genetic basis. Incomplete penetrance of mutations in all predisposing genes is reported, suggesting that a precipitating event or trigger is required to unmask the complement regulatory deficiency. The underlying genetic defect predicts the prognosis both in native kidneys and after renal transplantation[6]. Disease pathogenesis is related to dysregulation of the alternative pathway (AP) of the complement cascade at the level of the cell membrane secondary to mutations in a number of complement genes including complement factor H (CFH), complement factor H-related 5 (CFHR5), complement factor I (CFI), CD46 (MCP, membrane co factor protein), complement factor B (CFB), complement component 3 (C3) and thrombomodulin (THBD)[7]. Factor H has several important regulatory roles in the activity of the alternative pathway[8.] Mutations in complement factor H (*CFH*) account for approximately 25% of the genetic predisposition to aHUS. The familial recessive and dominant forms of HUS and the inherited deficiency of ADAMTS 13 and complement factor H probably predispose patients to developing HUS but do not cause disease per se, because these patients might not develop HUS until later childhood or even adulthood.In such cases, HUS is often triggered by an inciting agent such as an infectious disease[2].

With the finding that excessive activation of the alternative pathway of complement underlies the pathogenesis of aHUS in most patients, it became clear that complement inhibition would be a logical therapy. Eculizumab (a humanized monoclonal anti C5-antibody) is the only complement inhibitor currently licensed for any indication[9]. In aHUS, whether renal function returns is dependent on the extent of irreversible renal damage sustained before the onset of treatment. In both anecdotal reports and the trials it has been found that some patients who are on dialysis at the onset of the treatment will recover sufficient renal function to stop dialysis. This can take several months. Plasma therapy in the form of plasma exchange or plasma infusion has been the cornerstone of aHUS therapy since the 1980s and was essentially the only therapy available until recently. The effectiveness of plasma therapy is presumed to be related to its ability to deliver normal levels of CFH, CFI, CFB, and C3 and, when plasma is exchanged by apheresis, to remove mutant CFH, CFI, CFB, C3 and anti-CFH Abs[10]. Early diagnosis; promptness of TPE initiation and use of TPE as standard treatment in the setting of TTP-HUS is essential to avoid the high 30-day mortality rate[11].

In this case, child presented with acute gastritis, on admission, her platelet counts were normal, Hb was 6.5g%, total WBC count was 8600/mm^3. There was h/o haematuria for last 3 days, no h/o oedema, no h/o gastroenteritis, h/o sore throat 15-20 days back. She was very pale with mild icterus, liver 2cm palpable below the right costal margin, spleen not palpable. She was normotensive, urine output>1.5cc/kg/day. On investigations, we found that the child had deranged renal function- urea 93mg/dl, creatinine 2.7mg/dl, Na+ 127Meq/L, K+ 2.6Meq/L. LFT- bilirubin-3.6mg/dl, SGOT 80U/L, SGPT 75U/L, cholesterol 238mg/dl. Urine R/M-Proteins+, Pus cells 3-4/hpf, RBC: 40-50/hpf, Ep cells 1-2/hpf, Granular casts+, bacteria+. We were suspecting PSGN but pallor was out of proportion for a haematuria of merely 3 days.Also, she was icteric,which went against PSGN. We planned a peripheral smear which was suggestive of haemolytic anaemia, reticulocyte count of 28%. Hence, she was diagnosed to be a case of HUS inspite of normal platelet counts .Anti factor H antibody sent-came positive, confirming ATYPICAL HUS. She was started on i.v antibiotics for U.T.I, electrolyte imbalance corrected, B.P, urine output monitoring done. Her urea levels came down till 50mg/dl, but would not go below that, her creatinine levels averaged around 1.5mg/dl. Regarding UTI, She had relapsing remitting course of the disease. She had become so pale, that she had to be transfused with PCV on 4 different occasions. Child gave a history of breathlessness on exertion since 1 month that could be due to microscopic haematuria, which could not be picked up by the child; which indicates the relapsing remitting pattern of the disease. But, throughout the course of illness, her platelet counts never went below 1 lac/mm3.She was transferred to nephrology unit, where glucocorticoids were given in mega doses to suppress the complement pathway, but sadly the child developed cellulitis of the thighs and back and went into septic shock, before we could give her a trial of plasmapheresis. Promptness of TPE (Therapeutic plasma exchange) initiation is essential for patient survival since in those whose diagnosis is delayed are more likely to die than those promptly treated[12]. Hence, retrospectively, it may be said that starting plamapheresis in a case of atypical HUS may be a better option than to try on glucocorticoids.

According to the 2009 guideline of the European Pediatric Study Group for HUS[13], the first-line treatment of atypical HUS – i.e. HUS not mediated by enterohaemorrhagic *E. coli* (EHEC), and not associated with *Streptococcus pneumoniae* – should be plasma therapy (plasma exchange or plasma infusions) with early assessment of the clinical response.

4. PROGNOSIS

Diarrhoea associated HUS-<5% mortality in major medical centers, half of patients require dialysis in the acute phase. Most recover renal function completely, 20-30%have some level of chronic renal insufficiency, 5% remain dependent on dialysis[2].For non–Stx-HUS, patients have poor outcomes, with up to 50% progressing to ESRD or irreversible brain damage. As many as 25% die during the acute phase.

5. CONCLUSION

The first and foremost thing important is the diagnosis of atypical HUS, since its presentation has a wide range of clinical manifestations.Thereafter,Plasmapheresis should be started as early as possible in a case of atypical haemolytic uraemic syndrome. According to The European Pediatric Study Group for HUS expert recommendations for the treatment of patients with aHUS, plasmapheresis is to be started on daily basis for 5 days and then a graded decrease based on response. Plasma infusions(in case of complement factor deficiency) or exchange should be performed daily until the platelet count, LDH, and hemoglobin levels are substantially improved or even normalized or until an alternate treatment strategy has been decided upon. Renal function is an important marker to follow during the use of plasmatherapy, especially in the setting of acute renal failure. Eculimumab,the lone monoclonal antibody, approved for the treatment of aHUS, is being given once a week initially and then in every alternate day basis. As has been proposed by Loirat et al, plasma exchange would be a reasonable first therapy, with eculizumab introduced for nonresponse to plasma or with transition to the outpatient setting[14].

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