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A case of atypical HUS during maintenance phase of acute lymphoblastic leukemia: A stitch in time saves nine

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1. Introduction

Thrombotic microangiopathies are group of disorders characterised by microangiopathic hemolytic anaemia, thrombocytopenia, acute kidney injury (AKI) with or without neurologic abnormalities. Thrombotic thrombocytopenic purpura and hemolytic uremic syndrome are 2 major subtypes [1].Hemolytic uremic syndrome(HUS) is further classified as D + HUS and D- HUS depending on preceding diarrhoea. Etiologies of acquired D- HUS include streptococcus pneumoniae, malignancy (mainly solid tumours), chemotherapeutic agent, allogenic bone marrow transplant, systemic lupus erythematosus and viral infection (coxsackie, varicella, HIV) [2]. Atypical hemolytic uremic syndrome (aHUS) is a rare complication of hematolymphoid malignancies which requires urgent intervention, if untreated, has a high mortality rate of around 25%.Causes of aHUS in malignancy is multifactorial like infections, drugs and malignancy itself. Acute lymphoblastic leukemia is most common childhood hematological malignancy, which has a very good 5 year overall survival of about 80% in standard risk group patients [3].The course is complicated by infections, drug toxicity, refractory disease and relapse. Here we present a case of atypical HUS (aHUS), an unusual life-threatening complication during course of acute lymphoblastic leukemia (ALL) treatment.

2. Case

A 5-year-old boy, diagnosed as acute pre-B -ALL standard risk as per BFM 90 protocol, cytogenetics being trisomy 4,10,17, end of induction MRD negative, on maintenance phase since last 10 months. He presented with acute onset symptoms of fever, cough, breathlessness, irritability for 3 days with no history of bleeding, jaundice, or convulsions. On examination he was conscious but irritable, tachycardic, tachypnoeic, normotensive, pale and had fine crepitations over right upper lung fields. Investigations are as follows in Table 1.

Malaria, dengue, leptospira rapid tests were negative. Chest x-ray showed consolidation in right upper zone. Based on clinical presentation and initial investigations our suspicion was relapse in case of ALL with tumour lysis syndrome and pneumonia. But, the peripheral smear showed no blasts and instead had schistocytes 3+, micro spherocytes 2+. Coagulation profile was normal.

A diagnosis of atypical hemolytic uremic syndrome was made, secondary to pulmonary infection (community acquired), mostly suspicion of streptococcal infection. ADAMTS13, Anti ADAMTS13, Factor H and Anti Factor H levels were sent. ASO titre and anti DNAase was not sent due to financial constraints. Urine protein 1 + on card test, not quantified. Endotracheal tube secretions were negative for streptococcal infection. He was started on hemodialysis (HD), with RBC transfusion support and on broad spectrum antibiotics and oseltamivir. After an hour of HD, he developed hypotension with sudden onset respiratory distress, with chest X-ray suggestive of bilateral infiltrates. This event was suspected to be transfusion associated lung injury secondary to the packed RBC transfusion which he received during HD. This episode was managed with ventilatory support and inotropes. He was also started on injectable dexamethasone 4mg once a day since day 2. On day 5, when the blood pressure improved, he was started on therapeutic plasma exchange with single volume plasma exchange, which was 1.2 L for his body weight and hematocrit, exchanged with fresh frozen plasma with a femoral access with plasmaflux P2 filter alternating with alternate

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Table 1
Trend of investigations.

Day/Inv	1	5	11	14	18	21
Hb(g/dl)	4.0	5.0	4.5	5.8	7.6	9.3
TLC/ul	4200	3700	8500	5200	5540	6440
Platelet/ul	10000	20000	60000	50000	$2.25*10^6$	$2.27*10^6$
Reticulocytes (%)	20	14	10	6		4
LDH(IU/l)	4000	5301		1124		727
Haptoglobin(mg/dl)	<8					82
BUN (mg/dl)	95	60	45	38	40	28
Creatinine (mg/dl)	3.1	4.0	3.2	3.0	2.0	1.5
Indirect bilirubin (mg/dl)	3.2	2.8	2.5	1.5		0.7

hemodialysis. On day 11, he started improving, weaned and extubated. He underwent total of 7 cycles of hemodialysis and 7 cycles of therapeutic plasma exchange which were continued till platelet count normalised. Later his reports showed ADAMTS13 activity levels were low (35%), Anti-Factor H IgG antibody-positive with titre being 3000 AU/ml, *Anti*-ADAMTS13 IgM antibodies titre 200.

On day 24- patient had 1 episode of generalized tonic clonic seizure followed by sudden onset bilateral loss of vision. His MRI showed a hypertensive posterior reversible encephalopathy. This complication was suspected due to hypertension secondary to nephritis or due to steroids, followed by which his steroids were tapered rapidly and stopped by day 35. For hypertension, he was initially started oral amlodipine requiring maximum dose of 5mg/day, in view of persistent high BP readings on amlodipine, he was started on labetalol infusion 0.5 mg/kg/hr maximised to 0.8 mg/kg/hr, which he maintained his BP, while on tapering labetalol, he was started on oral clonidine at 0.4mg/day, oral labetalol at 2 mg/kg/day, oral prazosin at 0.1mg/kg/day 8 hourly and oral telmisartan 20mg/day which he required for 2 weeks gradually tapered and stopped in 6 months from the initial episode. His vision, CBC(complete blood count), renal parameters normalised by 2 weeks and was discharged with no neuro-deficit. He was restarted on his maintenance chemotherapy, clinically asymptomatic, normotensive, off antihypertensives, no neuro-deficit, no schistocytes in the peripheral smear, Hb: 11.5g/dl, leucocyte count: 3100/μl, platelet count: 2.4lakh/ul, creatinine: 0.8 mg/dl, urine protein: nil, ADAMTS13 levels 144%, ADAMTS13 antibody:<9.6 AU/ml and anti factor H antibody titre < 50 AU/ml

3. Discussion

Atypical hemolytic uremic syndrome (aHUS) is a variant of thrombotic microangiopathy (TMA) that is caused by abnormalities of the alternative complement pathway resulting in endothelial cell dysfunction and formation of microvascular thrombi. These could be due to inherited defects in the complement pathway or acquired due to antibodies to these factors secondary to infections like streptococcal infections, viral infections like HIV, varicella, chemotherapeutic agents, malignancies and transplant [4]. Most of the cancer associated TMA are seen mainly in solid malignancies. Hematological malignancies like acute lymphoblastic leukemia, non-Hodgkin lymphoma, myelodysplasia can also rarely complicated by TMA [5].The pathophysiology is abnormal angiogenesis in the marrow, aggressive growth of tumours and secondary myelofibrosis injuring the endothelial cell lining of the marrow vasculature by direct invasion, or as a result of chemotherapeutic agents.

Geoffrey Cheng et al. reported 2 cases of aHUS in children on maintenance chemotherapy, without any history of Ecoli infection managed with peritoneal dialysis and plasma exchange, relapsed after rechallange with 6 MP(6-mercaptopurine) and resolved with supportive care later 6MP was replaced by oral cyclophosphamide. In the second case it was related to influenzae infection. A heterozygous deletion of the CFHR3-CFHR1 genes was found in the first case [6]. Cavagnaro et al. also reported aHUS in a patient on maintenance chemotherapy secondary to CMV(cytomegalovirus) infection treated with gangciclovir and with no relapse on restarting maintenance chemotherapy [7].Kanchi et al. reported a case of recurrent HUS while the patient was receiving maintenance therapy for ALL and speculated a potential role for VCR(vincristine) and discontinued VCR from further cycles [8].Chandra et al. reported a child who developed HUS during induction therapy with VCR and L-asparaginase (L-ASP) [9].Clarke et al. reported HUS secondary to E.coli in a patient of ALL relapsed post allogenic transplant on VCR maintenance, and noticed no relapse of HUS on reinitiating VCR [10].aHUS has also been reported as preceding ALL ranging from 5 weeks to 5 months [11,12]. The characteristic features of these case reports are summarized in Table 2.

Our patient had pneumonia simultaneous with onset of atypical HUS, treated with plasma exchange and renal replacement therapy, with antibodies to ADAMTS 13 and anti-factor H and low ADAMTS13 factor and no recurrence of HUS on restarting maintenance chemotherapy including 6MP and VCR. We postulate HUS mostly secondary to anti complement factor H antibodies. The clinical course of post pneumococcal hemolytic uremic syndrome (pHUS) is typically more severe than diarrheal HUS, requiring more dialysis and supportive care. In 2008,Copelovitch and Kaplan reviewed all previous cases of pHUS and found a 12.3% mortality rate, with 10% progressing to end-stage renal disease, and 16% with chronic kidney disease and/or hypertension [13]. Management of pHUS is primarily supportive, with prompt administration of antibiotics, transfusions and renal replacement therapy. Plasma exchange should be done with 5% albumin and not FFP as the later worsens the condition with re-exposure to anti neuraminidase antibodies in donor plasma [13].Occurrence of atypical HUS in ALL apart from BMT(bone marrow transplant) setting can be multifactorial secondary to infections, chemotherapeutic agents and also can precede diagnosis of ALL. Atypical HUS requires urgent intervention in the form of renal replacement therapy and anti-complement factor 5 antibody i.e eculizumab. Role of therapeutic plasma exchange is not very clear but in case of anti-complement antibodies helps in clearing the antibodies [4].

Regardless of the cause, aHUS is a rare disorder with poor clinical outcomes, with a mortality rate of 25% and 50% of patients may show end stage renal disease (ESRD) [4].This case report drives the message that high suspicion of HUS and early diagnosis with a mere peripheral smear examination, and rapid start of treatment can be lifesaving and can revert long term organ damage.

Table 2

Clinical features/ authors	Geoffrey cheng et al. [6]	Geoffrey cheng et al. [6]	Cavagnaro et al. [7]	Kanchi et al. [8]	Chandra et al. [9]	Clarke et al. [10]	Our patient
Age	7year	3 year	2 year	5 year	4 year	21year	5 year
Previous diarrhoeal episode	No, negative for STEC	No, negative for STEC	No, negative for STEC	No, negative for STEC	No	Yes, proven to be Ecoli	No
Other infective etiology	Viral work up EBV, adenovirus, parvovirus, HHV6 negative	Influenzae A positive	CMV +	No	Blood culture: E-coli (Not O:157, negative to verocytotoxin)		Anti complement factor H antibody mediated
Presenting symptoms	Hematuria, vomiting, jaundice	Dark coloured urine, fatigue	Fever, irritability, dark coloured urine	Facial edema, hypertension	Hematuria, oliguria, with drowsiness	Jaundice, hematuria, proteinuria	Fever, breathlessness, oliguria, drowsiness
Association with acute leukemia	In maintenance treatment with daily 6MP, weekly methotrexate, monthly vincristine, 5 day/ month steroids	In maintenance treatment with daily 6MP, weekly methotrexate, monthly vincristine, 5 day/ month steroids	In maintenance treatment with daily 6MP, weekly methotrexate, monthly vincristine, 5 day/month steroids	In maintenance treatment with daily 6MP, weekly methotrexate, monthly vincristine, 5 day/month steroids	Induction treatment with vincristine, l asparginase, dexamethasone	In maintenance treatment with daily 6MP, weekly methotrexate, monthly vincristine, 5 day/ month steroids with intrathecal methotrexate	In maintenance treatment with daily 6MP, weekly methotrexate, monthly vincristine, 5 day/month steroids
Time between ALL diagnosis and HUS	10 months	31months	18 months	9 months	20 days	13 yrs	9 months
Association with chemotherapeutic agents	Yes 6MP, recurrence of HUS within 1 month of restarting 6MP	Not directly proven	No	Vincristine suspected	L asparginase suspected	No	No
ADAMTS13 levels and antibodies	Normal	Normal	Not done	Not done	Not done	Not done	Low(35%) AntiADAMTS13 positive Anti-factor H positive
Other work up	Renal biopsy:thrombotic microangiopathy	–	Renal biopsy: consistent with HUS and CMV infection	Renal biopsy: consistent with HUS	Renal biopsy: consistent with HUS	–	Renal biopsy not done
Genetic work up	Heterozygous deletion in CHFR3-CHFR1 genes	Not done	Not done	Not done	Not done	Negative	Not done
Treatment	Peritoneal dialysis, plasmapheresis, packed RBCS transfusion	Peritoneal dialysis, plasma infusion, packed RBCS transfusion	Dialysis, gancyclovir, labetalol for hypertension	Supportive treatment	Double volume plasma exchange with hemofiltration	Hemodialysis with RBC transfusion with hypertension management with nifedipine and furosemide	Therapeutic plasma exchange with hemodialysis, with supportive packed RBCs transfusion, and antihypertensives
Outcome/Relapse if any	within 1 month of restarting 6MP	Within 5 months of restarting maintenance,	No, completed rest of maintenance chemotherapy uneventfully	Within 5 months, 2 weeks post vincristine, so further vincristine withheld	Patient succumbed to intracerebral haemorrhage	No recurrence with restart of maintenance chemotherapy with normal renal functions	No recurrence with restart of maintenance chemotherapy with normal renal functions, ADAMTS13 levels: 144% (Normal),Anti factor H antibody titre < 50AU/ml

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