International Journal of Science and Research (IJSR)
ISSN (Online): 2319-7064
Index Copernicus Value (2015): 78.96 | Impact Factor (2015): 6.391

A Rare Presentation of Human Parvovirus B19 in a Child with Sickle Cell Disease: Case Report and Review of the Literature

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Abstract: ***A typical hemolytic uremic syndrome [aHUS] has been conventionally defined by the triad of microangiopathic hemolytic anemia, thrombocytopenia and renal failure without the known infectious triggers. It is considered as a form of thrombotic microangiopathy [TMA], the other form is thrombotic thrombocytopenic purpura[TTP]. A6 -year old Saudi boy who is a known case of sickle cell disease, was hospitalized for sequestration crisis. He developed acute renal failure, [ARF] accompanied by hemodynamic instability resulting from dehydration of gastritis and hypovolemia of sequestration crisis, thrombocytopenia, leukocytosis, and hemolytic anemia following a short episode of abdominal pain. In the next few days of, what initially appeared as typical splenic sequestration, and prerenal failure, this patient developed persistent renal failure after correction of dehydration and packed red cell transfusion. We report here a case of parvovirus B 19 infection that was complicated with hemolytic uremic syndrome that manifested by triad of (hemolytic anemia, thrombocytopenia and acute renal failure), in a case of sickle cell disease. Herein, positivity of parvovirus B19, a common cause of aplastic crises in sickle cell disease, was associated with HUS.***

Keywords: SCD, sequestration crises, HUS, parvovirus infection B 19.

Abbreviations:
SCD: sickle cell disease
HUS: hemolytic uremic syndrome
aHUS: atypical hemolytic uremic syndrome
TMA: thrombotic microangiopathy
TTP: Thrombotic Thrombocytopenic Purpura
FFP: freshen frozen plasma
PRBCs: packed red cell transfusion
MAHA: microangiopathic hemolytic anemia

1. Introduction

Thrombotic microangiopathy (TMA) in patients with sickle cell disease (SCD) is a rare complication. These patients manifest microangiopathic haemolytic anemia (MAHA) with laboratory evidence of haemolytic anemia, schistocytosis, and thrombocytopenia [1].Traditionally, HUS had been divided into diarrhea-positive and diarrhea-negative HUS. The former, also referred to as typical HUS. All other causes of HUS were referred to as atypical HUS or assigned to the diarrhea-negative HUS.

Currently, HUS is divided into: Primary causes without coexisting disease, such as cases due to complement dysregulation (also referred to as atypical HUS) [2], Complement gene mutations[3], antibodies to complement factor H and secondary causes: mainly due to infections or drugs.

Hemolytic-uremic syndrome is a leading cause of acute renal failure in infants and young children. It is traditionally defined as a triad of acute renal failure, microangiopathic hemolytic anemia and thrombocytopenia that occur within a week after prodromal hemorrhagic enterocolitis[4]. Atypical hemolytic uremic syndrome is called if these manifestatins occurred without the known infectious triggers a HUS is considered a form of TMA [5]

2. Case Summary

A 6- year old, Saudi boy, known as a case of sickle cell disease, was diagnosed 6 months back during an episode of pain crisis. He is on regular follow up, prophylactic antibiotics and folic acid. He presented with history of recurrent vomiting, he vomited meal content. It was non-projectile, non bilious vomiting, not associated with diarrhea or fever, not preceded by history of cough or runny nose.

On examination: looked unwell, lethargic, dehydrated with splenomegaly 4 cm below costal margin. Other systemic examination was unremarkable. He was admitted to pedia ward on 9 april 2017 as a case of sickle cell disease, gastritis, sequestration crisis and ARF..Lab result : HGB:4.3 g/dl, reticulocyte count:17%,WBC : 12.09 x10^9/L PLT: 158 x10^9/L [figure 1]. Renal function test showed high creatinine :121 mmol/l,and high BUN :9.9 mmol/l [figure 2], Na+:137 mmol/l, K+:4.4mmol/L. PTT was normal: 26.4,with a normal fibrinogen : 350 ug/L,while D-Dimer1.842 u/l was high, LDH :774U/L was high, liver function test : ALT:22U/L (normal), AST: 46U/L(high).

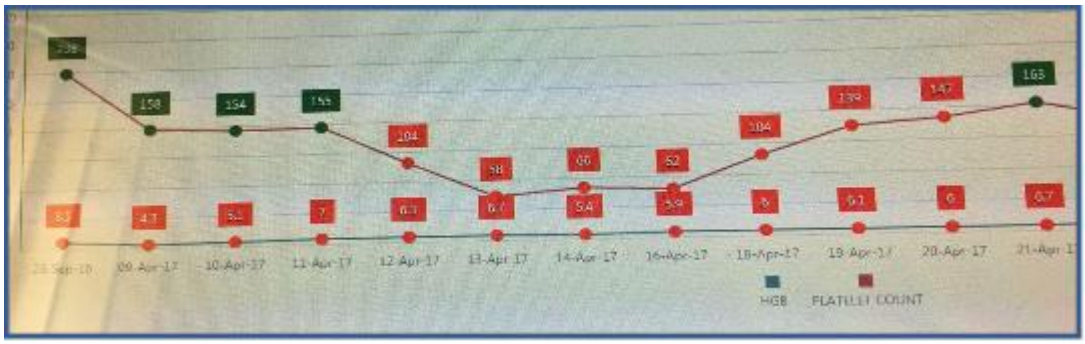


Figure 1: Showed trend of HGB &PLT throughout admission (HGB at time of admission was 4.3 g/dl &inspite of frequent blood transfusion, hemolysis ongoing and HGB not increase more than 6 g/dl, PLT initially was normal, on 3rd day of admission dropped while spleen regressed)

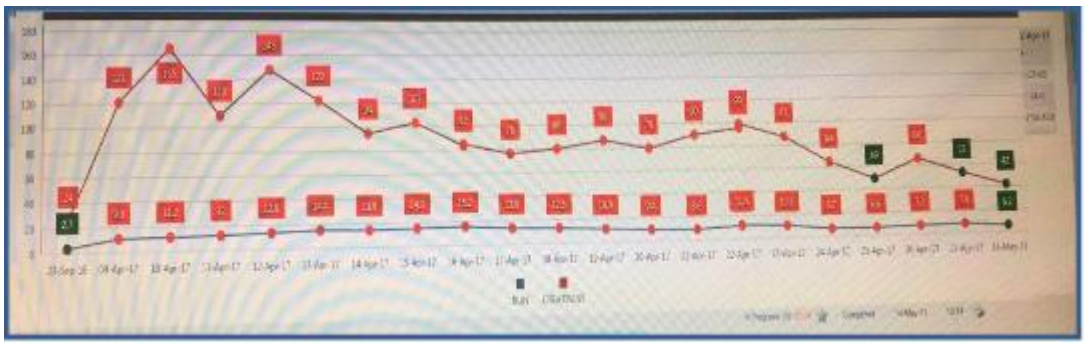
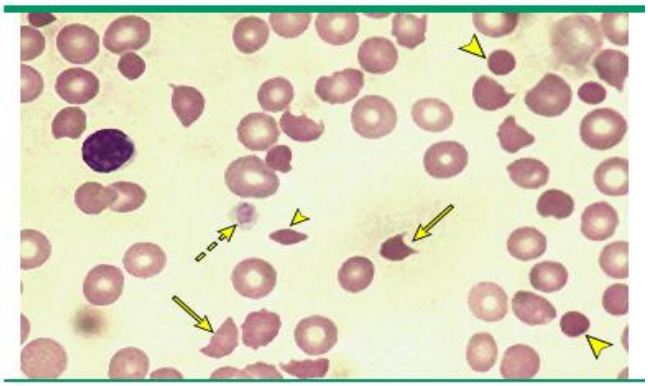


Figure 2: Showed trend of BUN & creatinin throughout admission

Management was initiated by hydration, PRBC's transfusion. Hospital course

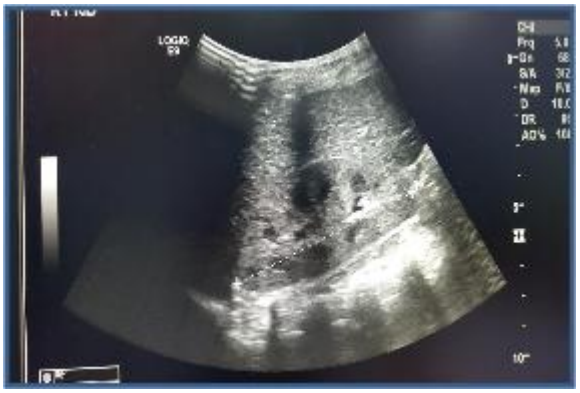
After hydration and PRBC'S transfusion, renal function was still impaired inspite of good hydration status. So,seen by pediatric nephrology team, and initial impression was pre-renal ARF secondary to dehydration VS sickle cell nephropathy. They adviced for fluid challenge test, sepsis work up and good antibiotic coverage, frequent assessment of clinical condition (hydration status) and laboratory results. Two days later, inspite of this management, still renal function was impaired. On 3rd day of admission (12 April 2017) while spleen was regressing, platelet dropped from 158 to 104 x 10^9/L, then to 55, 66, 62 x 10^9/L. There was ongoing hemolysis inspite of normalized size of spleen. Patient was seen by pediatric nephrology consultant and he diagnosed the case as HUS most likely atypical type.

Peripheral blood smear was requested as well as a sample for ADAMTS-13 to rule out TTP. Peripheral blood smear showed: normochromic normocytic anaemia with features of haemolytic anaemia, suggestive of microangiopathic hemolytic anaemia (MAHA).[picture 1]



Picture 1: Peripheral blood smear showed picture of microangiopathic hemolytic anemia MAHA (presence of schistocytes> 6%)

Abdomen US[picture 2] showed average size of kidneys (RT 7.4, LT 7.3 cm, bipolar), shape and parenchymal thickness of both kidneys showing mild increased echogenicity, accentuated medullary pyramids with slightly decreased cortico-medullary differentiation.



Picture 2: Abdomen US showed RT kidney

FFP was initiated twice / day, urgent referral to tertiary center was done, for possible renal biopsy as a case of atypical HUS and for genetic study and further management.

Patient developed fever in hospital, high grade, persistent & there was no clear source for this fever. So, sepsis work up and virology study were requested by pediatric ID team. Parvovirus B 19 result came +ve. Later on, ADAMTS-13 activity and antigen result came within normal range, so TTP was ruled out. All was in favor of aHUS (negative diarrhea, and not associated with known triggering systemic illness).

3. Discussion

To the best of our knowledge, this is a rare presentation of parvovirus B19 in SCD children
Few studies mentioned in literature that were similar to our case [5]

Hartel C, et al, 2007, reported renal complication associated with human parvovirus B 19 infection in early childhood in a previously healthy two- year old girl who presented with proteinuria and macroscopic hematuria.[6]

Orimo K, et al, reported prolnged anemia by superinfection of parvovirus B19 in a boy with entero hemorrhagic E.coli O157 – associated HUS in a 3- year old boy.[7]

Seward EW et al, 1999, reported HUS following human parvovirus infection in a previously fit adult.[8]

This particular case is further complicated by likely classification as 'atypical' HUS on the basis of his non-diarrheal presentation. Most commonly it is a secondary complication of intestinal infection with verotoxigenic *E. coli* O157 (or V-TEC), HUS is usually preceded by a diarrhoeal episode which was absent in this case.[9]The later laboratory results revealing a pronounced thrombocytopenia are more characteristic of HUS, as is the very low red blood cell Hb and highly elevated liver function tests, indicating liver involvement. HUS is also usually associated with raised creatinine levels, which remained raised after good hydration for the duration of this patient's supervision. In addition the increased reticulocytic count, however, was sufficient to change the focus of treatment to likely aHUS[10]

Among the factors which have been linked with a worsening prognosis of HUS, which can be fatal in 5 – 10% of cases, is pre-treatment with antibiotics. The early treatment of this case as possible sepsis, while entirely appropriate given the clinical presentation, may well have exacerbated the course of his illness. The authors would certainly not advocate reducing vigilance to the possibility of aHUS in young children with no diarrhea. It remains important to maintain an open verdict if the signs are not typical. This is especially apparent in the case of an atypical presentation of HUS which, although rare, is a serious and life threatening disease and delayed recognition or inappropriate treatment can significantly worsen the outcome.[11]

Finally it is still uncertain as to how this case should be classified. Several authors have made the distinction that non-diarrhoeal HUS should be considered as 'atypical' with a distinct pathology unrelated to bacterial infection and a genetic component involving complement factors. Other point of view is that, the presence of *parvovirus B19* should exclude this case as 'atypical HUS'. The distinction is an important one from the point of view of the patient, since non-typical HUS cases are susceptible to recurrence.

The severity of aHUS and its frequent non-specific presentation means that a high index of clinical suspicion must always be maintained for any similar case presenting without diarrhea.

4. Conclusion

We herein describe a case of aHUS that was misdiagnosed assequestration crisis with gastritis & ARF secondary to pre – renal cause (dehydration). This case stresses the fact that hemolytic anaemia, thrombocytopenia and ARF support HUS till proven otherwise. Significant value is added to this case because of positivity of human parvovirus B 19 which is a rare cause of HUS.

5. Consultations

- Pediatric nephrology
- Pediatric infectious disease
- Pediatric hematology

6. Consent

Written informed consent for publication of this case report and corresponding images was obtained from the patient's parents.

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