Pediatric Thrombotic Microangiopathy with AKI Secondary to aHUS : A Case Report

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ABSTRACT

TMA is a pathological process involving thrombocytopenia,microangiopathic hemolytic anemia and microvascular occlusion. TMA belongs to thrombocytopenia associated multi-organ failure(TAMOF) syndromes and therefore its diagnosis should be considered in critically ill children. MA is life threatening resulting from ischemic multiorgan failure and characterized by its diversity and high ICU mortality rate ~ 20%,despite appropriate treatment. It can manifest in diverse range of conditions and presentations, but AKI is a common prominent feature because of apparent propensity of the glomerular circulation to endothelial damage and occlusion. The most frequent TMA syndromes reported in children are haemolytic uraemic syndrome(HUS), in which renal impairment is the prominent clinical feature. Thrombotic thrombocytopenic purpura (TTP), another TMA syndrome also occurs in children often associated with cerebral involvement.(Secondary TMA are defined as TMA occurring with other co-morbidities serving as the triggering events. These include severe infections, autoimmunity, hematopoietic progenitor cells or solid organ transplantation, malignancy and drugs. Therefore the diagnosis of secondary TMA can be extremely challenging.

Here we present a diagnostic approach to a previously healthy 13Yrs old male child who presented in emergency with breathing difficulty, decreased oral acceptance, lethargy and altered sensorium for past one day, later found to have azotemia and anion gap metabolic acidosis.

Keywords: TAMOF; AKI; HUS; TTP; Azotemia

INTRODUCTION

The common features of TMA are microvascular thrombosis, consumptive thrombocytopenia and macroangiopathic haemolytic anemia(MAHA) leading to end organ ischemia and infarction affecting particularly kidney and brain.

Also in contrast to disseminated intravascular coagulation (DIC), TMA are usually associated with normal prothrombin time (PT), activated partial thromboplastin time (aPTT), factor V and fibrinogen.

Renal histological features of TMA on light microscopy include arteriolar and/or glomerular intracapillary thrombosis, often with accumulation of fragmented erythrocytes within capillary lumens, and focally ischemic or congested glomerular tufts. Severe arterial and arteriolar injury may be seen with or without widespread thrombosis, usually in the setting of malignant hypertension.

Despite overlapping clinical and biological features, TMA has its distinct pathophysiology and therapeutic management [1]. The most frequent TMA syndromes reported in children are haemolytic uraemic syndrome (HUS), in which renal impairment is the prominent clinical feature. Thrombotic thrombocytopenic purpura (TTP), another TMA syndrome, also occurs in children, often associated with cerebral involvement. Secondary TMA are defined as TMA occurring with other comorbidities serving as the triggering events. These include severe infections, autoimmunity, hematopoietic progenitor cells or solid organ transplantations, malignancy and drugs. Therefore, the diagnosis of secondary TMA can be extremely challenging [2,3].

Childhood haemolytic uraemic syndrome

Several types of HUS have been proposed. An infection-associated HUS is caused by Shigatoxin-producing Escherichia coli (STEC) strain and Streptococcus pneumoniae. STEC-HUS (~ 80–90% of HUS) usually occurs 5–10 days after a gastrointestinal

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infection (E. coli serotype 0157:H7 or O104:H4, mainly) and a prodrome bloody diarrhea; it is caused after hemorrhagic colitis and microvascular damage where the toxin enters circulation. Streptococcus pneumoniae -associated HUS (~ 5% of HUS), suspected after a history of pulmonary infection or meningitis, is due to the production of a neuraminidase responsible for cleaving the sialic acid of glycoproteins that exposes the cryptic Thomsen-Frieden Reich antigen. Atypical HUS (aHUS) (~ 5–10% of HUS) is mainly caused by an uncontrolled activation of the complement through the alternative pathway resulting from mutations in the genes encoding complement factor H (CFH), complement factor I (CFI), complement factor B (CFB), membrane cofactor protein (MCP), C3, and thrombomodulin (THBD), and autoantibodies against CFH or CFI [4,5]. Very rarely, aHUS are due to mutation in diacylglycerol kinase (DGKE) or deficiency of cobalamin C (cbl-C) [6,7]. The clinical presentation of aHUS is highly variable, but severe renal impairment is still the predominant feature.

Treatment of HUS depends on its aetiology and pathophysiological mechanisms. Treatment of STEC-HUS is largely supportive, including aggressive hydration and dialysis, with the aim to preserve renal function. However, in patients with neurological symptoms, plasma therapy (infusion of fresh frozen plasma or plasma exchange) may be considered. Recovery of STEC-HUS is usually spontaneous and the outcome is generally excellent [4,6,7]. Antibiotics (amoxicillin or third-generation cephalosporin) are needed in Streptococcus pneumoniae -HUS. aHUS is a recurrent disease associated with poor outcomes if not treated promptly. Genetic investigations are not required to initiate treatment [8]. Once STEC-HUS (stool culture or identification of shigatoxin), Streptococcus pneumoniae -HUS (in a proper clinical context) and TTP (normal ADAMTS13 activity) diagnosis are excluded, a monoclonal anti-C5 antibody (eculizumab) that blocks the activation of C5 should be considered as early as possible [9]. Plasma exchange is reserved for patients with autoantibodies against CFH or CFI. The time required to obtain the results of the biological investigations (usually a few days) should not delay plasma therapy. While plasma exchange is still used in many centres for HUS, it alone does not halt the progress of end-stage renal disease and requirement for renal transplantation, despite the improvement of haematological parameters [10]. The risk of anti-complement therapy includes meningococcal disease. Therefore, there is a longer-term risk of severe bacterial infection for which preventative strategies including immunisations and/or prophylactic antibiotics may be necessary in children prior to or receiving eculizumab therapy. Parenteral administration of hydroxo-cobalamin, folinic acid or betaine are the treatments of choice for aHUS associated with cbl-C deficiency.

CASE REPORT

An 11 years old boy reported to emergency department with complaints of decreased oral acceptance, vomiting ,lethargy and generalized oedema for past five days and altered sensorium for last 24 hours. On admission child appeared pale and edematous, was in altered sensorium. There was no preceding diarrheal or infectious disease history. No family history of any renal or hematological disease. On examination child was afebrile ,anthropometric parameters were between 50th and 90th percentile. His blood pressure was 130/80 mmHg, and his neurological status was E3V2M4(using Glasgow coma scale).On investigating the child; his Hb level was 5.47g/dl, reticulocyte count 16.6% platelets

-1,14,000/cu mm, serum sodium and potassium being 130 & 5.72 mEq/L respectively. BUN and creatinine levels were 126 and 12.62 mg/dl respectively. Total protein –el was 4.71g/dl, Serum albumin level was 3.2 g/dl. His C3 levels were decreased with normal C4 levels. Urinalysis revealed WBC-20-25/hpf, RBCs 80-90(Isomorphic),albumin 4+. ANA and ANCA being negative. His ASO titer was also negative. DCT and ICT showed negative results. LDH level-1076 U/L. Renal ultrasonography revealed B/L normal kidney size with altered CM differentiation. Child was presumptively diagnosed with AKI with Uraemic encephalopathy and urgent hemodialysis done following dialysis sensorium of the child improved with declining levels of BUN and creatinine. However anemia and thrombocytopenia persisted with worsening of renal function. BUN and serum creatinine being again on rising trend with gradually worsening oliguria, requiring repeated cycles of hemodialysis. Peripheral blood smear examination showed picture of hemolysis with abundant helmet cells with reduced platelet count ,suggesting of microangiopathic haemolytic anemia(MAHA). Kidney biopsy done which showed ischaemic glomerular changes including mesangiolysis, retracted tufts ,wrinkled pseudo thickened capillary basement membrane and RBCs fragmentation with severe Acute Tubular Injury with several necrotizing and Thrombotic Arteriolar lesions-TMA. Based on absence of preceding diarrheal illness, age of onset of disease and kidney biopsy findings of TMA ,abnormal activation of alternative complement pathway, aHUS (possibly of anti- CFH-aHUS) was considered the most likely diagnosis. Therefore Methylprednisolone pulse therapy (30 mg/kg/day) given for 3 consecutive days with immediate consideration of Plasmapheresis along with Monoclonal antibody-Eculizumab therapy. Unfortunately amid COVID situation as plasmapheresis could not be done at our institute, child was referred to other higher centre for plasmapheresis and further management.

DISCUSSION

The patient's initial clinical presentation including massive proteinuria, hematuria and azotemia indicated AKI with uraemic encephalopathy. To diagnose underlying cause of kidney injury relevant investigations sent, which revealed negative ASO titer with low C3 ,normal C4. General blood picture was suggestive of Microangiopathic haemolytic anemia –MAHA along with thrombocytopenia which fulfilled the clinical criteria for TMA. Kidney biopsy done which showed RBC fragmentation with ischemic glomerular changes with severe acute tubular injury with several necrotizing and thrombotic arteriolar lesions suggestive of TMA. Among the various etiologies of TMA, anti-CHF-aHUS was most likely diagnosis in this patient considering absence of proceeding diarrheal illness, abnormal activated alternative complement pathway and age of onset of disease. After diagnosing high dose corticosteroid Methylprednisolone pulse therapy given and Plasmapheresis was taken into immediate consideration and child was referred to another higher centre for the same on parent's request.

Approximately 50% of patients with HUS demonstrate genetic or autoimmune abnormalities causing dysregulation of the alternative complement pathway. CFH is the most commonly affected gene and patients with CFH mutations comprise 20-30% of all patients with a-HUS. The presence of anti-CFH autoantibodies causes functional deficiency of CFH. Anti-CFH-aHUS has been reported mainly in children aged 9-13Yrs ,although all age groups including infants and adults may be affected.

The mainstay of treatment for anti-CFH-aHUS during the acute phase is early initiation of plasma exchange to remove circulating autoantibodies and administration of corticosteroids and immunosuppressant therapy. A few case reports have described that eculizumab is effective in these patients;however further studies are necessary to establish the role of eculizumab in patients with anti-CFH-aHUS. The long-term prognosis of anti-CFH-aHUS is similar to that of other forms of aHUS. Patients show a high frequency of relapse (59%), chronic kidney disease (39%),end stage renal disease (27%) and death (9.5%).

CONCLUSION

An 11 Years old boy presented with microangiopathic haemolytic anemia, thrombocytopenia and AKI without preceding diarrheal illness. Low serum levels of C3 but normal levels of C4 indicated abnormal activation of the alternative complement pathway. Kidney biopsy confirmed histopathological picture of TMA. So after initial cycles of hemodialysis and later being diagnosed as a case of TMA by kidney biopsy; possibility of aHUS was kept and treatment with high dose steroids given with immediate consideration of plasmapheresis for which patient was referred to other higher institute as it could not be done at our center amid COVID situations. But unfortunately patient lost to follow-up. Clinicians should suspect aHUS and evaluate further in patients presenting with azotemia, anemia and thrombocytopenia without preceding diarrheal disease although it is very rare.

ETHICS APPROVAL

Our institution does not require ethical approval for reporting individual cases or case series.

INFORMED CONSENT

Informed consent for patient information to be published in this article was not obtained because our institution deemed that informed consent was not required as all information was de-identified.

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