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Case Report

Paediatrics Section

Atypical Haemolytic Uraemic Syndrome in an Infant with Ventricular Septal Defect: A Case Report

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ABSTRACT

Atypical Haemolytic Uraemic Syndrome (aHUS) is a rare type of thrombotic microangiopathy that occurs without Shiga toxin producing bacteria. It is a condition related to complement regulation, which may be genetic or acquired. The complement system's alternative pathway is commonly implicated, with around 6-10% of cases being caused by autoantibodies directed against factor H. While it typically affects children between 9 to 13-years-old, it can also occur in adults. Many patients do not have circulating Complement Factor H-related proteins 1 and 3 due to a homozygous deletion involving CFHR1 and CFHR3. Authors hereby report a case of a six-month-old female child who was diagnosed with Ventricular Septal Defect (VSD) at one and a half months of age. She presented with pneumonia and subsequently developed haemolytic anaemia with thrombocytopenia, oliguria, and acute kidney failure. She was diagnosed with Antifactor H antibody-mediated HUS. She was treated with plasma therapy, but the patient succumbed due to multiorgan dysfunction.

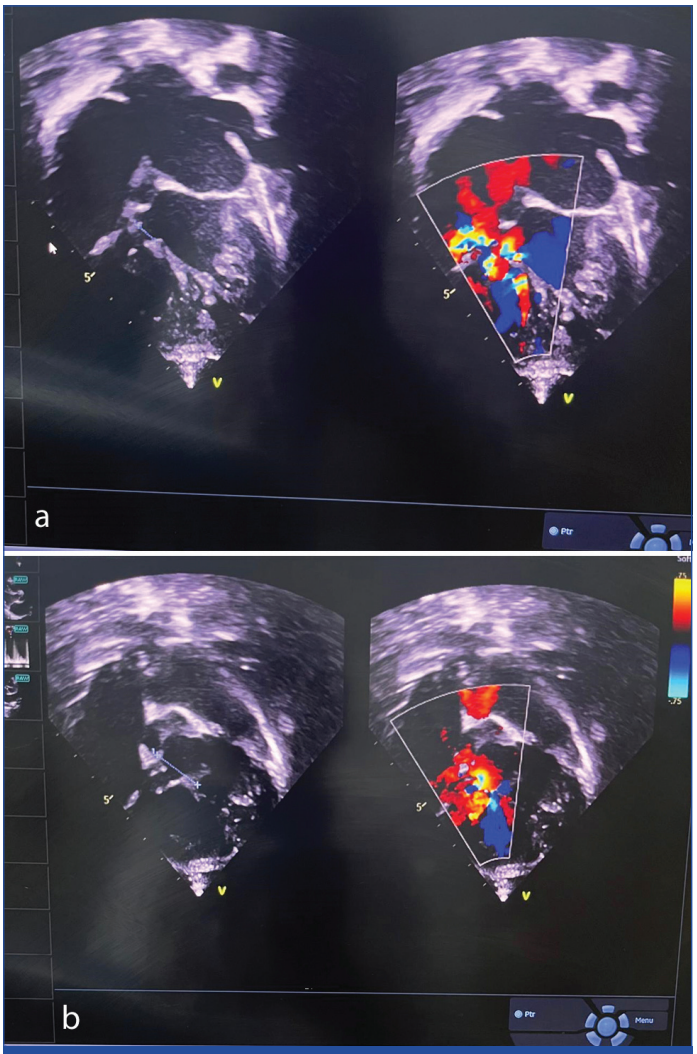
Keywords: Acute renal failure, Haemolytic anaemia, Thrombotic microangiopathy

CASE REPORT

A six-month-old female child, the firstborn of non consanguineous parents, presented with complaints of failure to thrive for four months, suck-rest-suck cycle for one month, along with increased work of breathing, cough, and cold for four days, and fever for two days. The child was diagnosed with a VSD at the age of one and a half months. Upon admission, the infant exhibited signs of cardiopulmonary compromise, including tachypnoea, cardiomegaly, and pulmonary oedema. Urine output was normal.

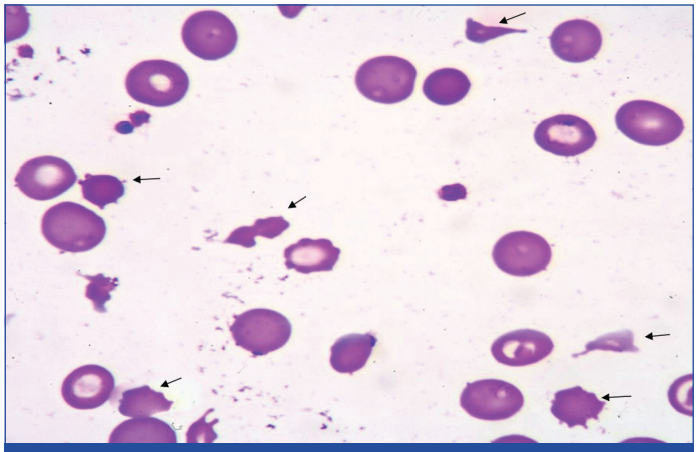
At three months of age, 2D echocardiography suggested multiple mid to apical muscular VSD [Table/Fig-1a,b] with Pulmonary Arterial Hypertension (PAH). The child was started on antifailure medications (furosemide, spironolactone, and hydrochlorothiazide) but was deemed inoperable. The child was put on a high-flow nasal cannula and started on i.v. antibiotics and antifailure therapy. Her haemogram indicated mild anaemia {Haemoglobin (Hb): 10 g/dL} with lymphocytic leukocytosis (16,900 cells/microlitre) and mild thrombocytosis (467,000 cells/microlitre). The following inflammatory markers were significantly elevated (D-Dimer: 580 ng/mL, Ferritin: 131.30 ng/mL, Fibrinogen: 148 mg/dL). Renal function tests showed mildly elevated urea (60 mg/dL) and creatinine levels (0.57 mg/dL). Lactate Dehydrogenase (LDH) was 303 U/L. Liver enzymes were within the normal range. The coagulation profile was normal. The initial blood culture did not show any growth.

Within days of admission, the infant's condition deteriorated rapidly. She developed ventricular tachycardia, necessitating mechanical ventilation and amiodarone infusion. The haemogram showed a decrease in haemoglobin (9 g/dL) and platelet (147,000 cells/microlitre) levels. Concurrently, acute kidney injury manifested with oliguria, haematuria, and hyperkalaemia, prompting the initiation of peritoneal dialysis. Her liver enzymes became elevated {Serum Glutamic-oxaloacetic Transaminase (SGOT): 173 U/L, Serum Glutamic-pyruvic Transaminase (SGPT): 483 U/L replace with}. On day 4 of the Intensive Care Unit (ICU) stay, the patient continued on mechanical ventilation and peritoneal dialysis. She had ongoing haemolysis with thrombocytopenia. eGFR was 26.6 cc/min. Her urea was 59 mg/dL and her creatinine was 1.37 mg/dL. Urine microscopy showed protein 2+, 70-80 Red Blood Cells (RBCs)/hpf, and 7-8 pus cells/hpf. She had nephrotic-range proteinuria (Urine protein: 360.4 mg/dL, Urine creatinine: 22.36 mg/dL, Protein/creatinine ratio: 16.12). Urine culture did not yield any growth. The clinical course was further complicated by hospital-acquired *Klebsiella pneumoniae* infection,



[Table/Fig-1a,b]: Multiple small VSD (Perimembranous and muscular) with left to right shunting.

prompting adjustment of antibiotic therapy. Peripheral Blood Smear (PBS) showed schistocytes and features of mild microangiopathic haemolysis [Table/Fig-2]. The Coomb's test was negative. Human Immunodeficiency Virus (HIV) and Hepatitis B surface Antigen (HBsAg) were negative. Dengue Immunoglobulin G (IgG), IgM, and Non Structural protein 1 (NS1) were negative. Her Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) antibodies were positive (2.45). C-reactive Protein (CRP) levels increased to 18.40 mg/dL. Her D-dimer level was >10,000 mg/L (ref: 0-500).



[Table/Fig-2]: Schistocytes (fragmented red blood cells) seen in Peripheral Blood Smear (PBS). (Different types of schistocytes like Burr cell, triangular cell and horn cells can be seen). Stain used- Leishman stain Power of magnification – 100x Oil immersion field.

Packed red blood cells were transfused to alleviate haemolysis. In the following days, she was weaned-off the ventilator and placed on a high-flow nasal cannula, gradually transitioning to room air. Despite upgrading antibiotics, the patient continued to experience fever spikes. Blood culture revealed the growth of Acinetobacter species, necessitating further antibiotic escalation. Peritoneal dialysis was discontinued after a week due to the development of abdominal distension. Plasma infusion was administered daily. While the patient's urine output improved throughout her hospital stay, her renal function tests continued to deteriorate, with serum urea rising to 128 mg/dL and serum creatinine to 2.72 mg/dL on Day 16. During peritoneal dialysis, the patient experienced hypokalemia (1.9 mmol/L on day 9 of ICU stay), which was corrected.

A repeat blood culture on day 11 revealed the presence of *Klebsiella pneumoniae* in central venous catheter samples. The serum procalcitonin level was 2.52 ng/mL (cut-off >2 ng/mL). On day 12 of the ICU stay, the patient was placed back on mechanical ventilation due to the development of respiratory distress. ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) activity was normal, ruling out Thrombotic Thrombocytopenic Purpura (TTP). Antifactor H antibody levels were measured at 11463 Au/mL (0-100), leading to the diagnosis of Antifactor H antibody-associated HUS. Genetic studies were not conducted due to resource unavailability. The patient's renal function continued to deteriorate. Further deterioration occurred as the patient developed Acute Respiratory Distress Syndrome (ARDS), resulting in a cardiac arrest episode on day 14 of her ICU stay. On day 17 of the ICU stay, she experienced pulmonary haemorrhage followed by another cardiac arrest episode, with resuscitation attempts proving unsuccessful as the patient ultimately passed away.

DISCUSSION

Haemolytic-Uraemic Syndrome (HUS) is characterised by a trio of microangiopathic haemolytic anaemia, thrombocytopenia, and acute kidney failure. It can be categorised into typical and atypical forms. Typical HUS is preceded by diarrhoea (D+ HUS) and commonly affects infants and children, with Enterohaemorrhagic E. coli (EHEC) being the leading cause in developed countries and Shigella dysenteriae type 1 in developing countries. aHUS, on the other hand, is not linked to antecedent diarrhea and may be familial or sporadic with genetic causes related to complement system dysregulation such as deficiency of factor H, factor I, factor B, thrombomodulin gene due to mutations, or autoantibodies against complement proteins. Inherited forms of the condition are known to affect individuals between the ages of 9 and 13, although they can also occur in adults [1]. It is often triggered by an infectious disease [2]. The present patient embodies a typical case of a factor H antibody-related aHUS with severe manifestations including arrhythmia, ARDS, and pulmonary haemorrhage resulting in respiratory failure. She experienced oliguria for approximately 10 days, which then resolved subsequently. Renal insufficiency ranges from mild to rapidly evolving into severe oliguric or anuric renal failure. Antibody-mediated HUS triggers symptoms such as pallor and weakness attributed to microangiopathic haemolytic anaemia. Severe hypertension often accompanies this condition. The combination of rapid renal failure along with intense haemolysis can lead to life-threatening hyperkalaemia. Patients presenting late exhibit profound neurological involvement with convulsions and occasional focal abnormalities [3].

HUS is a type of thrombotic microangiopathy, which occurs due to microvascular injury causing damage to the endothelial cells. Atypical HUS is a condition related to the regulation of the complement system. The alternative complement pathway's complement proteins are connected with complement-mediated HUS [4]. Variants in regulatory genes leading to loss-of-function or gain-of-function changes in an effector gene can cause this disorder [5]. In children with a gene variant(s), an infection may act as a triggering event, while antibodies to complement proteins may result in continual activation of the alternative pathway and formation of a membrane attack complex. Progressive platelet aggregation at sites of microvascular injury causes consumptive thrombocytopenia. Haemolysis arises from mechanical harm endured by red blood cells passing through damaged and thrombotic microvasculature. Mild endothelial injuries that would normally heal become aggressive microangiopathy due to inherited deficiencies in these factors [6].

Diagnosing the condition involves observing a mix of microangiopathic haemolytic anaemia with schistocytes [6], thrombocytopenia, and renal impairment. At the initial presentation, the anaemia is mild but progresses rapidly. Thrombocytopenia is consistently present in the acute phase, with platelet counts generally ranging from 20,000 to 100,000/mm^3. Both partial thromboplastin time and prothrombin times tend to be within normal ranges. Leukocytosis frequently occurs and can be significant. Urinalysis typically reveals microscopic haematuria and minor proteinuria. The severity of renal insufficiency can vary from slight increases in serum blood urea nitrogen and creatinine levels to acute kidney failure without urine production (anuric). A negative Coomb's test indicates no autoimmune involvement [7]. Determining the underlying cause of HUS involves evaluating family history for instances of HUS, previous episodes experienced by the individual, screening for Shiga-toxin-producing *E. coli*, assessing C3 and C4 levels, as well as ADAMTS13 testing to rule out TTP.

Key components of treatment encompass supportive measures such as addressing acute renal failure and managing hypertension if it is present. Plasma therapy, in the form of either plasma infusion or plasma exchange, represents one therapeutic avenue. Eculizumab, a Monoclonal Antibody targeting complement protein C5, has emerged as the preferred treatment for aHUS due to its favourable efficacy and safety profile [8]. It hinders the production of terminal components C5a and MAC C5b-9 [9]. The optimal duration for eculizumab treatment in aHUS remains unknown. Diagnosing aHUS presents challenges given its rarity and status as a diagnosis by exclusion. Patients with CFH variants exhibit the poorest outcomes among those with complement-mediated HUS [10]; individuals

carrying variants of the CFH gene typically progress to end-stage kidney disease within one year from onset. Kidney transplant might be an intriguing field of study and a method for reducing the effects of this disease in patients [11].

CONCLUSION(S)

aHUS attributed to antifactor H antibody is rare and seen in 6-10% of complement-mediated aHUS. Diagnosing aHUS is challenging because a significant number of patients, estimated to be between 30% and 50%, do not show any genetic or acquired mutations in the complement system. Thrombotic microangiopathy can develop due to conditions that activate the complement system. However, in recent years, Eculizumab has emerged as a game-changer in treating these patients. Timely detection and treatment are crucial to improving patient outcomes.

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