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Hemolytic uremic syndrome: A case report

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Abstract

Hemolytic Uremic Syndrome (HUS), is characterised by a triad of three main factors, microangiopathc haemolytic anemia, thrombocytopenia and acute kidney injury. Multiple aetiologies can cause this triad of symptoms; hence HUS is a group of disorders with similar clinical features. Paediatric age group is the most commonly affected, and STEC- HUS, which is HUS caused by E coli, which produces shiga like toxin, is the most common cause of infectious HUS in children. Though it has a multitude of etiological factors, Heamolytic Uremic Syndrome (HUS) as an entity has only a supportive treatment.

Case Report

A 4-year old male, of asian descent, was brought into the emergency department with abdominal cramps, vomiting and bloody diarrhoea that had started 24 hours before her admission. The patient was had vomited 4 times before he came in for admission, and was passing grossly bloody stools. The parents did not notice any precipitating events before the onset of symptoms, nor had he eaten anything out of the ordinary. On a detailed history and a physical examination, it was noted that the child was extremely dehydrated, did not tolerate oral feeds, irritable, with sunken eyes. No pallor, icterus or any skin rash was noted. The patient did exhibit tenderness, in the lower abdominal area, without rigidly, guarding or other signs that suggested peritonitis. Immediate intravenous access with 0.9% Normal saline was started and a diagnosis of gastroenterocolitis was considered initially, but as the patient's abdominal pain worsened, the possibility of a perforated appendix was considered. Immediate Laboratory tests were ordered- a complete blood picture with differential, serum urea, and creatinine, serum electrolyte levels, Lactate dehydrogenate levels, and a stool culture to confirm gastroenterocolitis, which is usually common, albeit in a less severe form in children of these ages. Imaging such as an erect abdominal X ray and an abdominal ultrasound were also performed, which were unremarkable Soon after his admission the patient appeared confused, hypotensive, despite an IV access for hydration, oliguric and laboratory findings were: Hemoglobin (Hb) 60 g/L, Hematocrit (Hct) 19%, Platelet count 43×10^9/L, White Blood Cell (WBC) count 17×10^9/L, Urea 16.6mmol/L, Serum creatinine 308 µmol/L, Creatine kinase 971 U/L, aspartate Aminotransferase (AST) 317 U/L, Alanine Transaminase (ALT) 276 U/L, C-Reactive Protein (CRP) 175.2 mg/L, Lactate Dehydrogenase (LDH) 3856 U/L, albumins 19 g/L, complement component 3 (C3) 0.5 g/L, complement component 4 (C4) 0.08 g/L,

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degree of *in vivo* hemolysis 50 mg/L. Stool culture grew out *E coli* O157:H7, classifying his case as typical HUS but what makes his case unique is that although the classic pathogen E coli was detected, the actual toxins, Shiga 1 and 2 toxins responsible for HUS were not detected. A genetic panel for atypical HUS genetic mutations were obtained and were pending during his hospitalization and eventually returned as normal

During the course of admission, he received multiple transfusions of packed red blood cells and platelets, his hypotension could not be stabilised even after continuous IV access, and he was started on pressor agents, dopamine was used to stabilise the blood pressure. Since he was oliguric despite continuous IV fluids, and a Foleys catheter was placed. By week 1 of his admission, since the onset of symptoms, his condition worsened, in addition to persistent anaemia and falling platelets, despite platelet transfusion and packed RBCs. The patient remained oliguric, with almost no urine in his Foleys bag, and his Arterial blood gas analysis showed mixed metabolic and respiratory acidosis, which points to renal failure. He also became dyspneic, and was started on oxygen, via nasal canula. On a chest X ray, mild pulmonary edema, and bilateral pleural effusions were seen. Soon after he started developing ascites thus pointing to worsening of the renal failure. These new symptoms, along with increasing levels of serum creatinine and blood urea nitrogen, which point towards acute kidney injury, called for starting renal replacement therapy-continuous hemodiafiltration with ultrasound guided venous access. It was planned to put the patient on about 10 days of dialysis, along with unfractionated heparin.

Unfortunately, during day 2 of dialysis, he passed away due to multisystem organ failure.

Discussion

Heamolytic Uremic Syndrome (HUS) is a condition consisting of a triad of definitive symptoms microangioathic haemolytic anemia, acute kidney injury, and thrombocytopenia. HUS, is basically a group of disorders, with multiple aetiologies, all leading up to the three main symptoms and their sequelae. The most common age group in which HUS is predominant is the paediatric age group, and more often, children under 5 years of age, of course, it may have varied ages of presentation, depending on the etiological cause [1]. Originally, Hemolytic Uremic Syndrome (HUS) was classified based on the presence of diarrhoea, as Diarrhoea Positive HUS (D+HUS) and diarrhoea negative HUS (D-HUS). However this has changed in the recent time, Now HUS is classified, clinically as Primary HUS, and secondary HUS.

Primary HUS is also referred to as atypical HUS, or the older Diarrhoea negative HUS, in which HUS due to complement deregulation [2]. Complement deregulation could be caused by Complement gene mutations, antibodies to complement factor H, inborn errors of cobalamin C metabolism and the rare Diacylglycerol Kinase Epsilon (DGKE) gene mutations. Complement mediated Hemolytic Uremic Syndrome (HUS) is caused by mutations in the genes involving complement proteins, mainly C3, and complement factors H, B, and I. Mutations in proteins involving the coagulation pathway, such as DGKE mutation, which are autosomal recessive, lead to primary HUS. It is thought that loss of function mutation of the *DGKE* gene, creates a prothrombotic state. Under normal circumstances, DGKE inhibits arachidonic acid-containing diacylglycerols, which activate protein kinase C. Another cause is the PLG mutation, PLG gene, codes for plasminogen and a Plasminogen deficiency leads to a reduced degradation of thrombi, and thus resulting in a prothrombotic state. The creation of the prothrombotic state in both these mutations, result in thrombi which is intravascular. The thrombi in small vessel beds, causes damage to Red Blood Cells, and release of inflammatory mediators, causing eventual endothelial cell damage, a hallmark of HUS. The more common secondary HUS, or typical HUS, is further divided into infectious and non infectious causes. The most common cause of HUS is Shiga toxin-producing Escherichia coli (STEC) (O157;H7)most commonly found in undercooked beef and it is one of the main causes of acute kidney injury in children under the age of 5 years. [1] The pathology involved is that, STEC-HUS is linked to glomerular thrombotic microangiopathy which can extend to the afferent arteriole. Kidney involvement in STEC HUS is noted in terms of thrombotic microangiopathy, cortical necrosis and arterioles and interlobular arteries predominant thrombotic microangipathy [3,4]. Other infectious causes of HUS include, strepotococcal pneumonia associated HUS, wherein the proposed pathology is that certain pneumococci display surface proteins which link plasminogen, forming plasmin and causing fibrinogen degradation, thus causing complement activation and finally endothelial cell damage. [5] Rare cases include HUS caused by viruses such as HIV and H1N1. Non infectious causes include drugs such as cyclocporine, tacrolimus, mitomycin C, which result thrombotic microangioapthy. Systemic Lupus Erythromatosis, especially with antiphospholipid syndrome, and pregnancy associated HUS are also included in this category [6].

Diagnosing Hemolytic Uremic Syndrome (HUS) is done clinically, based on the classical triad of microangiopathic hemolytic anaemia, thrombocytopenia, and acute kidney injury. HUS can be established by laboratory examination, such as a complete blood count, with differential, and peripheral blood smear, renal functions studies, and urinalysis. The microangiopathic hemolytic anaemia in HUS, can be confirmed with a haemoglobin and a hematocrit level, and this anaemia is typically Coobs negative in character. Moreover the peripheral blood smear is full of schistocytes, which represent fragmented red blood cells. The thrombocytopenia is defined as a platelet count below 140,000/mm^3 and is usually approximately 40,000/mm^3 in cases of HUS. Despite the low platelet count, there is no purpura or active bleeding. Lastly, the acute kidney injury, which may or may not lead up to renal failure, is one of the most of threatening features of HUS, and in most cases a renal biopsy is never required. Renal involvement varies from hematuria and proteinuria to severe renal failure detected by abnormally elevated serum creatinine and Blood Urea Nitrogen [BUN] levels) and oliguria.

In our patient, the most striking laboratory finding was extreme leukocytosis which persisted and the highest WBC count was 94×10^9/L. As no other signs of systemic bacterial infection or invasive mycosis were noticed, we believe that the increase in white blood cell number was linked to the systemic inflammatory response which was the reason behind his unfortunate demise. Another unique characteristic of our case was that, even though the characteristic E coli, o157:H7, was detected in the stools, there were no toxins detected which are responsible for the actual pathogenesis of the disease.

The aetiology and the type of HUS can be identified, using multiple lab studies, including but not limited to stool culture and examination, genetic analysis for mutations in genes such as DPKE and PLG, complement levels, mainly C3, and coagulation studies. Depending on the cause of hemolytic uremic syndrome

HUS, patients might present with additional clinical features such as CNS involvement, with strokes and multisystem organ failure, further evaluation must be done, especially in atypical cases to rule out condition with similar symptoms such as DIC, sepsis, TTP, and systemic vasculitis. Treatment in all cases of HUS is mainly supportive, in terms of managing thrombocytopenia, with platelet transfusions, variations in blood pressures with IV fluids and pressor agents, maintaining an electrolyte balance, treating falling heamtocrit values with packed RBS. For the more life threatening renal failure ie, rising creatinine and blood urea nitrogen dialysis is typically warranted. Depending on the type of HUS, some newer modalities of treatment are being tried such as Eculizumab in STEC HUC [7].

Conclusion

This particular patient warrants the need of a quick suspicion, evaluation and immediate supportive treatment of HUS, especially in the paediatric age group. Though prompt stool samples are necessary to establish the diagnosis, and rule out primary HUS, it is necessary that we don't wait to diagnose HUS till after the stool examination, as many atypical cases, like ours, shiga like toxins may not detected. Early diagnosis of this rare entity allows initiation of early supportive management, also reducing the number of unnecessary laboratory tests and treatments such as antibiotics. It is also necessary, to rule out other similar causes such as TTP, and sepsis, which although do cause some similar symptoms to HUS, do have a completely different mode of treatment.

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