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Hepatitis - E Associated Aplastic Anemia (HAAA) – A Therapeutic Quagmire: A Case Report

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ABSTRACT

Hepatitis associated aplastic anemia (HAAA) is a variant of Aplastic Anemia that is characterized by onset of pancytopenia with hypocellular bone marrow with increased levels of serum aminotransferases after an acute attack of viral hepatitis. Several viruses are linked to this disease including Hepatitis E. The pathophysiology is still unknown however it is believed to be caused by destruction of hematopoietic stem cells. Here we discuss a young male who developed HAAA, few weeks to month after his viral serology IgM for HEV came positive with deranged liver function tests.

Keywords: *Aplastic Anemia, HAA, Hepatitis E Associated Aplastic Anemia, Hep E And Aplastic Anemia Case Report, HAAA, Hep E – HAAA*

Background

Aplastic Anemia is defined as decrease in all blood cell lines with fatty/hypoplastic bone marrow. The underlying mechanism is believed to be caused by Cytotoxic T-lymphocytes mediated destruction of hematopoietic stem cells (Young *et al*., 2010). One such rare but well-known entity of Aplastic Anemia is Hepatitis Associated Aplastic Anemia (HAAA), in which bone marrow failure occurs secondary to at-least five times increase in serum levels of AST and ALT (Alshaibani *et al*., 2022). The disease was first diagnosed by Lorenz and Quaiser when they reported two such cases in 1955 (Lorenz and Quaiser, 1955). It accounts for 2% to 5% cases of aplastic anemia (Patel *et al*., 2017). Although in general AA does not appear to favor a particular race, age, or sex, HAAA has a slight male predominance and is more prevalent in adolescent males who present with pancytopenia 1-3 months after infection of viral hepatitis (Alshaibani *et al*., 2022; Patel *et al*., 2017; Wang *et al*., 2014; Osugi *et al*., 2007). HAAA usually presents in recovery window of acute hepatitis infection (Osugi *et al*., 2007; Osugi *et al*., 2007).

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The clinical manifestations of pancytopenia include anemia-related pallor, immunodeficiency owing to neutropenia and a higher likelihood of infection, and mucosal or cutaneous bleeding from thrombocytopenia. Intracerebral hemorrhage is the deadliest consequence of aplastic anemia (Alshaibani *et al*., 2022). The severe illness known as hepatitis-associated aplastic anemia (HAAA) has an 85% fatality rate (Rauff *et al*., 2011). While AA has been linked to HAV, HBV, and HCV in a small number of cases, non-A, non-B, and non-C viral hepatitis accounts for the majority of cases (Safadi *et al*., 2001). Immunosuppressive medications combined with HLA-matched bone marrow/stem cell transplantation is the definitive treatment for HAAA (Alshaibani *et al*., 2022). Immunosuppressive agents include both antithymocyte globulin (ATG) and cyclosporin. Many supportive therapies including platelets transfusion, leuko-reduced blood transfusions, hematopoiesis stimulation (granulocyte colony-stimulating factor (G-CSF), thrombopoietin receptor agonist (danazol) has shown positive results in delaying complications (Zhang *et al*., 2023; Li *et al*., 2022).

Case Presentation

We report a Punjabi, South Asian 23-year-old young male patient, who was admitted through medical emergency department with complaints of gum bleed and black tarry stool for 2 days, associated with fatigue, nausea, anorexia, and yellowish discoloration of sclera for one month. There was no accompanying pruritus, vomiting, hematemesis, lumps and bumps, abdominal distension, clay-colored stool, any urinary complaints and weight loss. There was no history of IV drug abuse, tattooing and prior history of jaundice. On presentation, he had a pulse of 110bpm, BP 100/70, temperature 101°F, and respiratory rate of 26 breaths/min. On further examination, he had pallor, jaundice, petechial rash over limbs, whereas systemic examination was unremarkable. The laboratory investigation showed: hemoglobin 7.3gm/dl, MCV 79.1 fl, total leukocyte counts 1.6x103/uL, absolute neutrophil count (ANC) 526 cells/ul, platelets 2x103/uL, reticulocytes count 0.3%, along with marked hypochromasia and without any atypical cells. While his ALT, AST and LDH levels were 587U/L and 317U/L (more than 20 times raised) and 220 respectively. His vitamin B12, folate, direct and indirect Coomb's test were normal.

Serological tests for hepatitis (A, B, C), Epstein–Barr virus, parvovirus B19, herpes, and HIV were negative except for hepatitis E IgM and IgG which were reactive. Patients was also found negative for Anti-Nuclear Antibody (ANA), Anti Mitochondrial Antibody (AMA), Anti Smooth Muscle Antibody (ASMA), Anti Parietal Cell Antibodies. Abdominal ultrasound confirmed mild hepatomegaly. Adequate length trephine biopsy of bone marrow confirmed hypocellular bone marrow with cellularity only 15%, along with hyperplasia of adipose components and no infiltrates of lymphoma, primary or metastatic tumor was seen at tested site. Fanconi Anemia by mitomycin C stress test and Paroxysmal Nocturnal Hemoglobinuria

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through cytometric immunophenotyping was also excluded. Hence, patient was diagnosed as a case of Hepatitis E associated Aplastic Anemia.

He was initially treated with supportive therapy including broad-spectrum antibiotics, blood products, filgrastim 300mcg S/C once daily and eltrombopag 150mg orally once daily for 1 month. But patient did not exhibit spontaneous remission of cytopenias while his liver function tests were normalized. Therefore, his allogenic bone marrow transplant was advised, but it was delayed due to HLA-matching and financial constraints. Meanwhile, immunosuppressive therapy was initiated consisting of oral prednisolone 1mg/kg/day, and cyclosporine 10mg/kg/day after consultation with infectious disease, hematology and oncology department. Unfortunately, it was withheld after 3 weeks due to opportunistic infection. Then, broad-spectrum antibiotics were initiated, including piperacillin/tazobactam 4.5g IV thrice daily, gentamicin 80mg IV thrice, vancomycin 1g IV twice daily and oral voriconazole 200mg twice daily. His condition continued to deteriorate and remained on invasive ventilatory support for 1 day due to respiratory failure. But he didn't survive.

Limitations in this case included delay in HLA-matching, high cost of treatment and lack of availability of medications.

Conclusion

This case report underscores the importance of considering aplastic anemia in the context of hepatitis E, raising awareness within medical community. Considering high mortality associated with Hepatitis E Associated Aplastic Anemia, the decision of hematopoietic stem cell/bone marrow transplantation should be made at earliest. However, in developing countries like Pakistan, many factors including patients' interest, cost and availability of medical facilities pose a hurdle. In such conditions, immunosuppressive therapy along with supportive therapy should remain the treatment of choice for such patients.

Discussion

WHO recognizes Hepatitis E (HEV), a disease of developing nations, which spreads through fecal-oral route due to improper sewerage lines and scarcity of clean drinking water (Shahzad *et al*., 2001). According to recent investigations, it is the most predominant etiological agent for sporadic hepatitis in Pakistan. A cross-sectional study conducted in Pakistan in 2019 found that the overall prevalence rates of anti-HEV IgG in males and females were 19.23% and 4.77%, respectively (Farooqi *et al*., 2022). Though

Hepatitis E is a self-limiting disease but it does not provide life-long immunity (Shahzad *et al*., 2001; Malik, 1987). Common clinical manifestation of hepatitis E includes fatigue, fever, abdominal pain, nausea, vomiting, cholestasis and jaundice. It can also present with wide range of extrahepatic complications including neurological, renal, hematological and rheumatological (Webb and Dalton, 2020). A rare but distinct form of aplastic anemia, hepatitis E-associated aplastic anemia (HAAA) arises weeks to months following an acute bout of self-limited hepatitis. Whereas severe aplastic anemia is defined by bone marrow hypocellularity <25% with at least two of the following: ANC <500/ µL, platelet <20000/ µL or retic count <60,000/ µL. (Davies and Guinan, 2007) After developing severe bone marrow aplasia, the average survival period is two months, and the fatality rate varies between 78% and 88% (Gonçalves *et al*., 2013). In Pakistan, until now only one such case is reported in 2011 (Rauff *et al*., 2011).

This patient presented with pallor, jaundice and bleeding tendencies. There was mild hepatomegaly on ultrasound, in absence of spleen or lymph nodes, which is similar to other studies and previous cases reported of HAAA. Immunosuppressive medication and allogeneic bone marrow transplantation are the available treatments for HAAA. If a HLA-identical donor is available, bone marrow transplantation using hematopoietic stem cells is favored over immune suppressive medication. However, in this case matched sibling donor is unavailable, immunosuppressive therapy would be the preferred treatment option (Mohseny *et al*., 2021). We started immunosuppressive therapy while his HLA matching for Bone marrow transplantation was in process. However due to poor socioeconomic status and lack of availability of other drugs in our country, only azathioprine, cyclosporin with prednisone was used which proved to be unsuccessful. At the time when his HLA was matched to his sibling, patient already had developed opportunistic infections which included pneumonia and urinary tract infections. His health continuously deteriorated despite use of culture sensitive broad-spectrum antibiotics and antifungals, which culminated in his death.

Declarations

Ethical Approval and Consent to Participate: Yes, taken

Availability of Supporting Data: Yes, Available

Consent for Publication: Yes, Taken

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