Hepatitis-associated aplastic anaemia: A case report from a tertiary care facility of Pakistan
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Abstract
Hepatitis-associated aplastic anaemia (HAAAA) is an uncommon variant of aplastic anaemia which may present as acute or chronic, mild and transient or fulminant disease. The development of aplastic anaemia is usually fatal if not treated in time, with mortality rate being as high as 85%. A high index of clinical suspicion is required for the diagnosis and exclusion of acquired forms of aplastic anaemia. Here we present a case of a 28-year-old male who presented with sero-negative hepatitis and rapidly progressive bone marrow failure who was given a trial of Granulocyte Colony Stimulating Factor followed by a successful allogenic bone marrow transplant.

Keywords: Hepatitis associated aplastic anaemia, Liver injury, Bone marrow transplantation.

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Introduction
Hepatitis-associated aplastic anaemia (HAAAA), though a rare complication of viral or toxic liver injury that leads to significant morbidity and mortality, accounts for nearly 5.4% of all acquired aplastic anaemia cases worldwide. Most of these cases are preceded by an episode of idiopathic hepatitis, with common hepatitis viruses (including Hepatitis A-C, E, G, Epstein-Barr virus, Cytomegalovirus (CMV), parvovirus B19 and echovirus) accounting for only 6% of the cases, and in majority of the instances specific aetiology of acute hepatitis could not be identified on clinical and serologic basis. Aplastic anaemia usually occurs weeks or months after hepatitis with as many as 10% of the cases developing aplastic anaemia after more than a year. The typical patient is a young male with 15 years as the median age of diagnosis. The mean five-year survival following haematopoietic stem cell transplant for HAAAA has been reported to be 82% and the 10-year survival with immuno-suppressants is 69%, showing a tremendous improvement in the management of HAAAA. The most common causes of death in HAAAA are bleeding and infections, with spontaneous resolution seen in some patients.

Here we report the case of a 28-year-old male who presented with hepatitis followed by severe aplastic anaemia that required multiple transfusions and immuno-suppressant therapy. The patient's consent was taken for publication of the case report.

Case Report
A 28-year-old married man presented to the Emergency Department of Pak Emirates Military Hospital, Rawalpindi, in September 2018, with generalised weakness, malaise, decreased appetite and nausea for the last five days, followed by clinical jaundice after 2 days and then a high grade intermittent fever with epistaxis, gum bleeding and a vesicular eruption involving buccal mucosa after another two days. There was no history of exposure to drugs or toxins, radiations, animals, any recent illness or contact and travel. He was vitally stable, fully oriented, afebrile, clinically pale and icteric with multiple petechial and vesicular eruptions involving buccal mucosa, a liver of 3 cm below the right costal margin but no splenomegaly.

His haematological and biochemical development is depicted in the Figure-1. On presentation, his haemoglobin was 12.5g/dl, Total Leucocyte Count (TLC) 1.3 x 10^9/L with 57% neutrophils, platelets 20 x 10^9/L, a retic count of 0.2%, slide for malarial parasites was negative, total bilirubin 659 umol/L with direct bilirubin of 464 umol/L, Alanine Transaminase 2491 U/L, Alkaline phosphatase 189 U/L, Prothrombin Time was 15 seconds, C Reactive Protein 12mg/dl, Coomb's test and autoimmune profile were negative. Serological tests were negative for anti HAV IgM, Anti HEV IgM, HBsAg, anti HCV antibodies, HBe antibodies, Cytomegalovirus IgM, Epstein-Barr virus IgM, HIV IgM and IgG, Parvovirus B19, Dengue and Brucella. Polymerase Chain Reaction (PCR) was negative for CMV, Herpes Simplex Virus (HSV) I/II and Congo virus. Ultrasound of the abdomen showed a hepatomegaly of 17cm with normal echotexture.
Clinically, the patient did not respond to supportive treatment, including blood product transfusions and empiric antibiotics as a neutropenic regimen and his bicytopenia rapidly progressed to severe pancytopenia with further worsening of Liver Function Tests (LFTs). Bone marrow aspiration showed a hypocellular marrow with diluted trials. It was followed by a bone marrow trephine biopsy that again showed a hypocellular bone marrow with no evidence of granulomatous inflammation or malignancy (Figure-2).

Thus, a diagnosis of Hepatitis-associated aplastic anaemia (HAAA) was made and the patient was referred to a dedicated haematology unit. He was given a trial of Granulocyte Colony Stimulating Factors that did not generate any response. The patient underwent a successful allogenic bone marrow transplant from a sibling and his recovery has been uneventful during six months after transplant.

Discussion
HAAA is a rare variant of acquired aplastic anaemia predominantly presenting in young males with bone marrow failure after weeks to months following an episode of hepatitis. The incidence is relatively higher for Eastern population, reflecting higher prevalence of hepatotropic viruses in these countries. Clinical features and experimental data strongly suggest that bone marrow failure is secondary to immune-mediated mechanism, though viral serologies are negative in majority of the cases.

HAAA is treated with allogenic bone marrow transplantation as the first line of treatment and in cases where HLA matched sibling is not available, immuno-suppressant therapy, including anti-Thymocyte Globulin and Cyclosporine, is advocated. Broad spectrum antibiotics should be started empirically without waiting for laboratory isolation of organisms, and systemic antifungals should be added early if fever fails to respond to antibiotics. Granulocyte Colony Stimulating Factors (G-CSF) are usually ineffective but a short course can be given in severe infections. Corticosteroids are only used for serum sickness as they are ineffective as an immuno-suppressant drug. HAAA can also lead to long term complications such as Myelodysplastic syndrome, Paroxysmal Nocturnal Haemoglobinuria and Acute Myeloid Leukaemia.
Conclusion
HAAA is an uncommon variant of aplastic anaemia which may present as acute or chronic, mild and transient or fulminant disease, thus a high index of clinical suspicion is required for the diagnosis and exclusion of acquired forms of aplastic anaemia. The development of aplastic anaemia is usually fatal if not treated in time, with mortality rates as high as 85%. Our patient had a successful allogenic bone marrow transplant after an unsuccessful trial of Granulocyte Colony Stimulating Factors.

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References