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Hepatitis-Associated Aplastic Anemia: A Case Study on Hematopoietic Crisis and Clinical Implications

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Abstract: ***Background**: Hepatitis-associated aplastic anemia (HAAA) is a rare but severe condition marked by bone marrow failure following acute hepatitis, often with an unknown aetiology. This study aims to present a rare case of Hepatitis-Associated Aplastic Anemia, outlining its clinical progression, treatment challenges, and potential interventions to improve outcomes. This case study presents a 48-year-old contract labourer who developed HAAA after an episode of seronegative hepatitis. Initial treatment focused on managing liver dysfunction; however, progressive pancytopenia led to a fatal deep neck infection. This report highlights the critical need for early diagnosis, bone marrow transplantation, or immunosuppressive therapy to improve patient outcomes. **Case Presentation**: A 48-year-old male contract labourer presented with a one-week history of progressive fatigue, jaundice, dark urine, pruritus, and abdominal discomfort. Initial investigations revealed elevated liver enzymes (AST: 778 U/L, ALT: 1317 U/L) and hyperbilirubinemia (TB: 7.66 mg/dL). Serology for hepatitis A, B, C, and E was negative. Imaging demonstrated hepatomegaly with periportal cuffing and a thickened gallbladder wall. He was diagnosed with acute viral hepatitis of unknown etiology and treated with ursodeoxycholic acid, hepatoprotective agents, and antihistamines. At follow-up, the patient presented with new-onset pancytopenia, petechiae, purpura, and fatigue. Bone marrow biopsy revealed hypocellularity (5-10%), confirming severe aplastic anemia. Despite supportive management with transfusions, antibiotics, and antifungal prophylaxis, the patient's condition deteriorated due to febrile neutropenia and a deep neck infection following a dental procedure. This led to airway obstruction and a fatal outcome. **Discussion**: HAAA involves immune-mediated destruction of hematopoietic cells, with cytotoxic T-cell activation as a key mechanism. First-line therapy includes allogeneic bone marrow transplantation (BMT) or immunosuppressive therapy (IST) for those without a matched donor. Early diagnosis and intervention are crucial, as delayed treatment and secondary infections are associated with poor prognosis. **Conclusion**: HAAA should be considered in patients with acute hepatitis and subsequent pancytopenia. Early BMT or IST, along with rigorous infection prevention, is essential to improve outcomes.***

Keywords: Hepatitis-associated aplastic anemia, Bone marrow transplantation, Pancytopenia, Cytotoxic T cells, Immunosuppressive therapy

1. Case Presentation

Patient History: A 48-year-old male contract labourer from Bellari presented to the hospital with complaints of progressive fatigue and a significant decrease in tolerance to daily physical activities, such as walking up one flight of stairs or performing routine tasks like bathing. These symptoms had been ongoing for one week and were associated with jaundice (yellowish discolouration of the skin and eyes), dark urine, and generalised pruritus, which was severe, worse at night, and disrupted sleep. He also reported a vague sense of abdominal bloating and fullness for four days prior to presentation.

During the preceding three days, the itching intensified, and the patient's quality of life was significantly impaired. There was no history of abdominal pain, nausea, vomiting, diarrhoea, or constipation. He denied any weight loss, fever, respiratory distress, facial puffiness, or reduction in urine output. There was no history of bleeding manifestations, including hematemesis, melena, or bleeding gums.

Past Medical History:

- No history of hypertension, diabetes, tuberculosis, asthma, or any other chronic illnesses.
- No earlier surgeries or blood transfusions.
- No history of substance abuse, including alcohol, tobacco, or intravenous drug use.
- No high-risk sexual behaviours or recent tattooing.

- Denied any history of prolonged medication use or allergies.
- Mixed diet; noted a reduction in appetite since the onset of symptoms.

Family History:
- No family history of similar illnesses or hematologic disorders.
- All family members were reported to be in good health.

Examination on Admission:
a) General Examination: Icterus (++), multiple excoriation marks on bilateral upper limbs due to pruritus.
b) Vital Signs: Pulse: 96 bpm, BP: 110/70 mmHg, SpO2: 98% on room air.
c) Systemic Examination:
   - CVS: S1 and S2 heard, no murmurs.
   - RS: Bilateral normal vesicular breath sounds, no added sounds.
   - Abdomen: Soft, non-tender, no hepatosplenomegaly, bowel sounds present.
   - CNS: Conscious, oriented, no focal neurological deficits, no flapping tremors.

Table 1: Blood investigations of the patient (first and second admissions)

CBC	30/10/24	20/12/2024	LFT	30/10/24	1/11/2024
HB	14.1	5.8 gm			
PCV	44.3	15.3	TB/DB	7.66/6.65	9.6/7.2
RBC	6.05 million	1.55 million	Total Protein	6.2 gm	6.8 gm
MCV	87	94 fL	Albumin	4.2 gm	4.2 gm
MCH	36	32.4	AST	778 U/L	743 U/L
MCHC	35.4	34.5	ALT	1317 U/L	1213 U/L
RDW	12.9	17.2	ALP	210 U/L	188 U/L
TLC	6650	1230	20.12.2024 LDH – 130 D- DIMER – 0.4 PT – 12.4 INR – 0.94 aPTT – 31.0 VIT. B12 – 581 FOLIC ACID – 9.4		
DLC	54/33/1/12/0	19/78/1/7/0			
PLATELET COUNT	2.7 lacs	0.13 lakhs			

Negative for – Hepatitis A, B, C, E.
Negative for – Malaria, Weil felix and Dengue.
Urine Routine – Within Normal Limits

UsG Abdomen and Pelvis-

Liver – normal echo texture

CBD – Proximal CBD measures 5 mm, Borderline Prominent.
Minimal central IHBRD. Calcified Granuloma in Left lobe of Liver measuring 3mm.

GB – Partially distended with thickened wall of about 5mm, no calculi
Spleen- measuring 13 cm, enlarged in size

CT Scan of the Abdomen (Plain and Contrast)

History: To r/o hepatic abscess / 2Hilar growth

Protocol: Helical sections from the level of dome of the diaphragms to the symphyss pubs in 128 slice
MDCT scanner.

Findings:
Liver: Measures 17.7 cm, enlarged in size, normal in outline and attenuation. No focal lesions seen.
IHBR are not dilated. CBD is normal. Portal vein measures 14 mm, dilated. Minimal peri-portal cuffing noted. A well-defined hyperdense focus measuring 2.5 mm is noted in segment VII of right lobe of liver -? Calcified granuloma. Tongue like projection of the left lobe of liver noted - Beaver tail (Normal anatomical variant).

Gall Bladder: Minimally distended. Wall is thickened and edematous.

Spleen: Measures' 12cm mildly enlarged in size. Normal in outine and attenuation.

Pancreas: It is normal in size, outline and attenuation.

RIF: No evidence of focal colection or mass lesion seen.

Others: The visualzed bowel bops are normal, Major abdominal vessels are normal. Few subcentimetric mesenteric lymph nodes noted.

No e/o free fluid in the abdomen. No e/o gut wal thickening/ mass lesion in the abdomen.

Vertebrae show spondylotic changes. Atherosclerotic calcified plaques noted in the arch of aorta and its branches.
Impression:
- Hepatomegaly with peri-portal cuffing; Thickened and edematous GB wall - * Suggested LFT correlation to rule out hepatitis.
- Mild splenomegaly.

Clinical Course:
First Admission and Management: The patient was diagnosed with acute viral hepatitis (non-A, B, C, E) and discharged on ursodeoxycholic acid, hepatoprotective agents (metadoxine, silymarin, L-ornithine L-aspartate), and antihistamines. He was advised regular follow-ups.

Follow-Up (3 weeks): He reported improved appetite, resolution of itching, and overall better health. However, blood investigations were deferred to the subsequent visit.

Subsequent Presentation (1.5 months post-discharge): The patient returned with complaints of painful swallowing for 10 days, easy fatigability, exertional dyspnea, and light-headedness for one week. He noted easy bruising, non-itchy petechial rashes on his extremities, and a single-day episode of high-grade fever with chills and night sweats.

Examination on Re-Presentation:
a) General Examination: Icterus (+), petechiae and purpura over extremities, purpura at the base of the tongue.
b) Vitals: Pulse: 96 bpm, BP: 110/70 mmHg, SpO2: 98% on room air.
c) Systemic Examination:
- CVS: S1 and S2 heard, ejection systolic murmur over the pulmonary area.
- RS: Bilateral normal vesicular breath sounds.
- Abdomen: Soft, non-tender, no organomegaly.
- CNS: Conscious, oriented, no focal neurological deficits.
- Bone Marrow Aspiration and Biopsy:
- Hypocellular marrow (5-10% cellularity) with markedly reduced hematopoietic lineages.
- No evidence of blasts, granulomas, or abnormal cells.

Management:
- He was admitted for febrile granulocytopenia and pain in the oral cavity due to gingival ulcerations. Microbiological analysis of throat swab revealed Enterococcus faecalis in low number of copies. He was treated with antibiotics, antifungal and antiviral prophylaxis, and adequate oral hygiene. Oral surgeon was consulted and alveotomy of the 8th teeth of mandible on the right side was performed because of impacted teeth with pericoronitis
- Received 2 units of PRBC and 8 units of RDP.
- Referred to a haematologist, who recommended bone marrow transplantation.

2. Discussion

The Camitta criteria, which include BM cellularity <25% and two of the subsequent criterion—neutrophils <0.5 × 10^9/L, platelets <20 × 10^9/L, and reticulocytes <20 × 10^9/L—define severe AA [1].

A rare kind of AA that follows an AH attack is called HAAA. Most instances are seronegative for hepatotropic viruses, while it may occur after viral infections such as HIV, hepatitis A, B, C, G, EBV, CMV, parvo B19, echovirus, and transfusion-transmitted virus [2,3,4,5]. According to studies, only 6% of cases have a viral origin [2]. In addition to being documented in individuals who received orthotopic transplantation for nonviral hepatitis [7], HAAA was also linked to toxic liver injury [6].

After a period of seronegative acute hepatitis, the patient developed severe aplastic anemia during liver function recovery.

According to research on the immunopathogenesis of HAAA, the liver is the first organ targeted by an antigen-driven T cell expansion [8]. When BM fails, both the liver and the blood experience infiltration of clonal and non-clonal T cells, which manifest as a skewed T cell repertoire [8]. Early on, common cytotoxic T lymphocytes (CTL) identify target antigens in BM cells that are comparable to those in the liver. This leads to the selective clonal development of CTL that are highly tropic to BM, which is followed by the destruction of BM cells later on [9].

CTLs generate IFN-γ, which causes necrosis and cell death by themselves and through the initiation of a cytokine cascade, ultimately preventing hematopoiesis [4]. Immunohistochemical staining of liver biopsies demonstrates buildup, confirming this, revealing accumulation of CTL in HAAA patients, as well as increased proportion of HLA DR-positive CD8 cells (which are considered to be activated CTL) and decreased CD4/CD8 ratio in their peripheral blood [3,4,10].

CD8-expressing Kupffer cells may be important mediators of HAAA [11]. Response to immunosuppressive therapy (IST) has been proven by replacement of broad skewing pattern of T cell distribution to normal [8,9]. Our patient had plentiful T lymphocyte infiltrate in BM specimen, as well as in peripheral blood, with low normal CD4/CD8 ratio.

Without treatment, HAAA inevitably results in death. Allogenic BMT from an HLA-matched sibling is the first line of therapy [4]. Studies show that the average survival rate following BMT is 70% at 10 years and 82–86% at 5 years [2,4,12].

Antithymocyte globulin (ATG), antilymphocyte globulin, Cys, and cyclophosphamide are all part of IST, which is only given to individuals who do not have an HLA-matched sibling donor [5,16–18]. The preferred course of treatment combines growth factors with Cys and ATG. With intensive combined IST, the 10-year survival rate is expected to be between 69 and 88% [1,14], with a mean response rate of 70 to 80% [3,13,14].

Age above 20 and postponed treatment are the two biggest determinants of survival, according to Locasciulli et al. [1]. Individuals with extremely severe HAAA (<0.2 × 10^9/L) require more time to respond to therapy [14]. Despite the possible hepatotoxic effects of Cys and ATG, which may potentially enhance liver function by suppressing T cells, it is advised not to postpone IST [14].

BMT from an unrelated, HLA-matched donor is an alternative for individuals who do not react to IST [1,7]. Because of the possibility of interstitial pneumonitis, prophylactic treatment for CMV is advised [14]. Lamivudine, telbivudine, or entecavir are recommended antiviral

prophylactics for individuals with HBsAg- or anti-HBc-positive status [7]. Severe infections and cerebral bleeding are the leading reasons of death [10,12,14].

He was admitted for febrile neutropenia while our patient and the donor were undergoing pretransplant evaluation. He got a retromolar trigone abscess, and the infection progressed to the deep tissues of his neck, obstructing his airway. Infections in the neck's potential spaces and fascial planes are referred to as deep neck infections (DNI). Since 70% of adult cases of DNI are caused by odontogenic infections, it is likely that the dental operation our patient had two weeks prior served as the entry point.

Immunosuppression, low socioeconomic level, and comorbidities are risk factors for the development of DNI, and the primary isolated pathogens are Streptococci, Enterococci, and Staphylococci. Airway obstruction, pneumonia, sepsis, Lemierre's syndrome, necrotizing cervical fasciitis, and descending necrotizing mediastinitis are the most common side effects. Broad-spectrum antibiotic treatment is required, typically in conjunction with surgery.

Our patient had supportive measures, antibiotics, and surgery, but his condition worsened and ultimately resulted in death.

In conclusion, the development of HAAA must always be taken into account while treating patients with AH, typically during the stage of improved liver function. Treatment and diagnosis delays are important predictors of survival. The mainstays of treatment for patients without an HLA-matched sibling donor are BMT or IST.

Because AA patients are more prone to infections, extra care should be taken when it comes to odontogenic infections, which can result in DNI and other potentially fatal consequences. Given the high mortality risk associated with delayed diagnosis, this case highlights the importance of early intervention and rigorous infection prevention in patients with suspected HAAA.

Early intervention with bone marrow transplantation or immunosuppressive therapy remains essential for improving survival in patients with Hepatitis-Associated Aplastic Anemia.

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