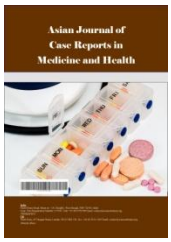

Asian Journal of Case Reports in Medicine and Health

5(1): 110-116, 2022; Article no.AJCRMH.89341

Case Report: Hepatitis-associated Severe Aplastic Anemia of Unknown Etiology

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/89341

Case Study

Received 20 May 2022
Accepted 25 July 2022
Published 30 July 2022

ABSTRACT

Aplastic anemia (AA) is a life-threatening, autoimmune-mediated condition that targets bone marrow precursors leading to pancytopenia. Hepatitis-associated aplastic anemia (HAAA) is one of the rarest entities where the recovery of acute hepatitis is complicated by aplastic anemia. Hepatitis viruses (A-E, G), non-hepatitis viruses (cytomegalovirus, Epstein-Barr virus, HIV, Parvovirus B19, and echoviruses,) and drugs/toxins have been recognized as etiological agents. We present a case of a 29-year-old Asian male presenting with progressive jaundice, diagnosed to have acute cholestatic hepatitis, subsequently leading to severe aplastic anemia without an identified inciting agent.

Keywords: Acute hepatitis; aplastic anemia; hepatitis-associated aplastic anemia; idiopathic.

1. INTRODUCTION

Hepatitis-Associated Aplastic Anemia (HAAA) is a rare, acquired subtype of aplastic anemia, where the bone marrow aplasia is preceded by an episode of acute hepatitis [1]. HAAA is usually seen in males including adolescent boys and young aged men [2]. The presumed etiology for acute hepatitis includes hepatitis viruses (A-E, G), non-hepatitis viruses (cytomegalovirus, Epstein-Barr virus, HIV, Parvovirus B19, and echoviruses), and rarely drugs/toxins. However,

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in most cases, the inciting agent could not be identified on clinical and serological grounds and thus regarded as idiopathic [3,4].

Severe aplastic anemia(SAA) is defined “as a bone marrow cellularity less than 25-30 percent of normal or less than 50 percent normal cellularity in which fewer than 30 percent of the cells are hematopoietic and at least two of the following are present: absolute neutrophil count<500/microliter, platelet count <20,000/microliter, or absolute reticulocyte count <60,000/microliter” [5]. SAA occurrence following acute hepatitis is 0.03-0.2%. This clinical entity requires an expeditious diagnosis and appropriate treatment as it is a perilous condition with 85 percent of universal mortality [6].

2. PRESENTING CONCERNS

A 29- year-old apparently healthy driver presented with progressive yellowish discoloration of eyes for three weeks duration with dark urine for 2 weeks without pale stools or associated pruritus. He had a low-grade intermittent fever associated with malaise, loss of appetite with weight loss of ~2 kg over one month duration. He denied right hypochondriac pain or abdominal pain radiating to back.

He denied inflammatory type arthritis, photosensitivity skin rash, recurrent oral ulcers or alopecia. There was no preceding history of pruritus or sicca syndrome and no associated chronic blood and mucus diarrhea, alternative buttock pain. He denied gradually worsening psychiatric symptoms or abnormal movements. There was no history of recent onset hyperpigmentation, diabetes, joint pain, or evidence of sexual dysfunction.

He consumes meals from roadside shops, but mostly home-cooked meals prepared with proper hygiene. He denies high-risk sexual behavior or intravenous drug use or a history of blood transfusions. He denied the use of prescription, non-prescription, or illicit drugs.

3. CLINICAL FINDING

On admission, examination revealed a thin built, febrile, ill looking male who was pale, deeply icteric without lymphadenopathy or organomegaly. During the hospital stay, the patient developed easy bruising and one episode of spontaneous gum bleeding on day 5. He developed a high swinging fever, and productive cough with whitish sputum without significant respiratory distress on day 8. He also complained of painful oral ulcers on the 10th day of his hospital stay

3.1 Diagnostic Focus and Assessment

Infective etiology, mainly viral or an atypical bacterial or autoimmune aetiology (Autoimmune hepatitis, primary biliary cirrhosis, or an overlap syndrome) was considered as the main differential diagnosis. We considered toxins and malignant disease with liver and bone marrow involvement as probable differential diagnoses.

His initial biochemical evaluation revealed an acute liver injury with raised bilirubin and liver enzymes with a normal coagulation profile. (total bilirubin (T Bil) of 301.9 umol/L, direct bilirubin of 190.5 umol /L, alkaline phosphatase (ALP) 94U/L, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) of 2209 and 1195 U/L, respectively).

The baseline serological workup for autoimmune, infectious, or metabolic causes of the liver disease were ruled out. The basic radiological workup including an ultrasound abdomen did not reveal any evidence of biliary obstruction. His laboratory investigations showed an improvement of the liver profile and the development of pancytopenia towards the latter part of hospital stay (Table 1).

Initial acute hepatitis work up did not reveal any etiological diagnosis. (Table 2) and we were unable to proceed with liver biopsy due to rapid progression of marrow failure.

Bone marrow aspiration and biopsy revealed normal bone trabecular architecture with marked hypocellular marrow spaces occupied with fatty tissue with less than ten percent of cellularity without any abnormal cell infiltrates or fibrosis, meeting the diagnostic criteria for severe aplastic anemia (Fig. 1) Examination of the aspirated bone marrow showed normal karyotype, peripheral blood did not show diepoxybutane-induced chromosomal breakage and excluded Fanconi anemia. Haematological work up was performed in order to rule out other causes for aplastic anemia.

Table 1. Investigation summary chart

	Day 1	Day 14	Day 21	Day 35	Day 39
wbc ×1000/mm^3	6	2.21	0.24	0.41	0.24
rbc ×1000/mm^3	5.18	2.81	2.05	1.45	1.00
Hb g/dl	12.7	8.4	8.0	7.5	5.4
plt × 1000/mm^3	156	6	3	4	3
ANC × 1000/mm^3	3.53	.05	.015	.023	0.08
cre	98	80	89	96	76
CRP	<5	<5	12	78	143
PT-inr	1.13	1.02	1.00	1.2	1.4
Ast IU/L	1195	1312	171	91	35
ALT IU/L	2219	2407	454	188	45
D.bil	190.5	215	164	128	40.5

(WBC: white blood cell, RBC: Red blood cell, ANC: absolute neutrophil count)

Table 2. Etiological evaluatuion- summary chart

Hepatitis B antigen and hepatitis B antibody	negative
Hepatitis A IgM	negative
Hepatitis C IgM	negative
Hepatitis E IgM	negative
Hepatitis G	Not done
HIV 1 and 2	negative
CMV IgM and IgG	negative
EBV IgM	negative
Mycoplasma pneumoniae IgG	Equivocal [0.83(<0.8=negative)]
Mycoplasma pneumoniae IgM	negative
Enterovirus PCR	negative
ANA	1:80 (positive)
DsDNA	negative
Anti-mitochondrial antibody (AMA)	negative
Anti liver kidney microsomal antibody	negative
Anti smooth muscle antibody	negative
IgM level	42mg/dl (47-147)
IgA	116mg/dl (47-147)
IgG	1052 mg/dl (569-1919)
Serum complement levels C3	108 mg/dl (55-120)
Serum complement levels C4	35 mg/dl (20-500)
Serum ferritin	2670,9164 µg/L (30-620)
Serum iron	236 µg/dL (65-175)
Total ion binding capacity	242 µg/dL (250-450)
Transferrin saturation	98% (20-50)
Unsaturated iron binding capacity	6 µg/dL(150-350)
Serum fibrinogen level	1.4 g/L
Serum triglyceride level	149 mg/dL (<150)

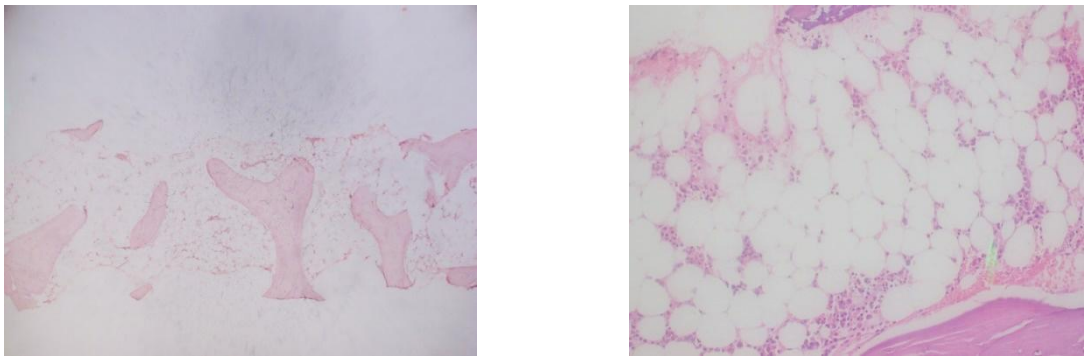

Fig. 1. Bone marrow picture

The diagnosis was made as severe hepatitis associated aplastic anemia without identifiable aetiology.

3.2 Therapeutic Intervention

After admission, initially patient was managed for acute hepatitis of unknown origin, and he was started on intravenous N- acetyl cystein infusion which continued till his liver enzyme normalized. With the development of pancytopenia, he was treated with prophylactic platelet transfusion, bufficoat and irradiated pack cells as needed. He was isolated and barrier nursing was introduced.

Pending the autoimmune antibodies, we tried a trial of oral steroid which was abandoned due to poor response and the risk of infections.

Filgrastim (colony stimulating growth factor), broad spectrum antibiotics and anti-fungal were continued.

Once the bone marrow results were available, we excluded the possibility of Fanconi anemia and as the patient was in severe marrow suppression the immediate decision for Immune Suppression Treatment (IST) was taken since matched-sibling haematopoietic stem cell transplantation was not an option.

He initially received five doses anti thymocyte globulin (ATG) with methyl prednisolone then started on oral prednisolone.

3.3 Follow Up and Outcome

Eight days after commencing ATG treatment, patient developed high fever spikes while receiving broad spectrum antibiotics, antivirals, and antifungals. Despite all these measures patient deteriorated and succumbed due to multi-organ failure secondary to pneumonia caused by multi-resistant strain of *Klebsiella pneumoniae.*

4. DISCUSSION

HAAA is rare, life threatening, acquired, autoimmune haematological condition preceded by an episode of acute hepatitis. The first two cases of HAAA were reported in 1995 by Lorenze and queasier [7].

Our patient was a young male which agrees with the characteristic stereotype of this rare disease entity. Characteristically, the patients develop severe pancytopenia two to three months after an episode of acute hepatitis and usually with the resolution of hepatitis [1,7] Our patient developed evidence of bone marrow failure within 2 weeks from first presentation, and within two months of initiation of his symptoms. Also, several studies have suggested that there is no precise duration gap between the onset of bone marrow failure and acute hepatitis, it could vary from less than year to less than three months [8,9]. In the typical course of illness, aplastic anemia usually develops after completing of partial resolution of acute hepatitis which agrees with our patient's presentation as well. Acute hepatitis does have variable presentation with a clinically benign course.

Various hepatitis and non-hepatitis viruses have been attributed as the aetiology of HAAA, though in most cases aetiology is uncertain [10]. There are some reports of drug induced liver injury (DILI) leading to HAAA. We screened our patient with all the available serological testing in order to exclude typical hepatitis viruses including A, B, C, D, E, and G and for available non hepatitis viruses as Parvovirus B-19, Cytomegalo virus, Epstein-Barr virus, Transfusion Transmitted Virus (TTV), echo virus and Entero virus.

The immunopathogenesis of HAAA is described as CD8/cytotoxic T cell mediated mechanism leading to increased levels of interferon gamma (INF-γ) and tumour necrosis factor (TNF-α) affecting bone marrow and liver cells [11].

HLA matched sibling haematopoietic stem cell transplantation has been proved as the first line treatment strategy for HAAA with a mean response rate of 85%. Current practice is to treat with immunosuppressive therapy with cyclosporine and anti-thymocyte immunoglobulin (ATG) when the matched sibling donor bone marrow transplantation is unavailable.[11] Immune suppressive treatment has 70% response rate and by using combination regimes of ATG, cyclosporin, corticosteroids and haemopoietic growth factors have improved response rates up to 75% [10,7].

HAAA contributed to 3.3% of SAA. Profound neutropenia in SAA leads to higher susceptibility for infections and higher mortality [11]. The immune suppression treatment yields another major risk factor for invasive bacterial and fungal infections. Nosocomial infections caused by coagulase negative *staphylococcus spp*, related to central venous catheters are frequent while gram negative bacteria being uncommon [7]. In our patient's immune compromised state led to sepsis secondary to resistant nosocomial strain of *Klebsiella pneumoniae* which resulted in multi-organ failure and death.

5. CONCLUSION

HAAA is a life threatening, acquired clinical entity which is unfamiliar to most physicians. The condition requires urgent diagnosis and prompt appropriate management due to high mortality.

Due to variety of etiological factors, it could be quite challenging for a physician to identify underlying etiology.

PATIENT CONSENT

Patient's family provided written consent for this case report.

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s)

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/89341