

Bone marrow aplasia in Haemophilia-A with Hepatitis-C and human immunodeficiency virus co-infection: A case report

Shabneez Hussain¹, Izza Hussain², Aqsa Ashfaq³, Laila Abdul Karim⁴, Shoukat Mirza⁵, Hasnain Zafar⁶

Abstract

Haemophilia A is an inherited bleeding disorder caused due to the deficiency of factor VIII. This case report of a 17-year-old HA boy co-infected by hepatitis C (HCV) and human immunodeficiency virus (HIV) followed by bone marrow aplasia seeks to address the key clinical question of the causality and management of bone marrow aplasia in a resource-constrained setting. Our patient developed pancytopenia which prompted the diagnosis and management of HCV and HIV. Bone marrow biopsy revealed severe aplasia. He was treated with highly active antiretroviral therapy (HAART). Two years later, he developed septic arthritis and haemarthrosis of the elbow and knee joints. He underwent arthrotomy of the knee joint. The patient expired, postoperatively, due to septic shock. This case underlines the need for truly universal access to virally inactivated replacement therapy to prevent complications secondary to infections transmitted by transfusion.

Keywords: Haemophilia A, Inherited bleeding disorders, Bone marrow aplasia, Hepatitis C, Human immunodeficiency virus.

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Introduction

Haemophilia A is an X-linked recessive bleeding disorder caused due to the deficiency of factor VIII, with a prevalence of 1 in 5,000 male live births. Patients mainly suffer from deep tissue bleeding such as joint, gastrointestinal tract, or intracranial bleeding. The treatment is either plasma-derived factor VIII or recombinant factor VIII concentrates. In low middle-income countries, haemophilia A patients are mainly treated with cryoprecipitate and fresh frozen plasma or plasma derived factor VIII concentrate, depending on its availability.¹

In Pakistan, HCV (30%) is the most prevalent transfusion-transmitted infection in patients with haemophilia A as compared to HBV (0.4%) and HIV (0.1%), while co-infection

with HCV and HIV is very rare (0.001%).¹ It is well known that HIV contributes to the worsening of liver disease in patients infected with HCV.² Additionally, HCV can increase the risk of progression to acquired immunodeficiency syndrome despite highly active antiretroviral therapy (HAART).²

Although autoimmune haemolytic anaemia secondary to HCV³ and coinfection (HCV and HIV) in haemophilia patients has been reported,⁴ bone marrow aplasia due to HCV and HIV co-infection in haemophiliacs has not been documented. We describe the case of a haemophilia A patient with co-infection of HCV and HIV, who developed bone marrow aplasia and later succumbed to its complications.

Case Report

We describe the case of a 17-year-old haemophilia A patient (not receiving prophylaxis with factor VIII concentrates), who presented with anaemia and thrombocytopenia in October 2015. Baseline complete blood count (CBC) showed haemoglobin (Hb) 8.7 gm/dl (reference range 12.3 – 16.6 mg/dl), haematocrit (Hct) 25.2% (reference range 38.4 – 50.7%), mean corpuscular volume (MCV) 103 fl (reference range 78.7 – 96.3 fl), mean corpuscular haemoglobin (MCH) 35.7 pg (reference range 25.1–31.6), total white blood cell count (WBC) 5.5x10⁹/L (reference range 3.5–12 X 10⁹/L), absolute neutrophil count (ANC) 4.3 X 10⁹/L (reference range 1.5–8x10⁹/L) and platelet count 7x10⁹/L (reference range 154–433x10⁹/L). The spleen was not palpable on physical examination while ultrasound of the abdomen showed normal spleen span (8.7 cm).

He had been diagnosed with moderate haemophilia A at the age of four years. There was no history of suspected sexual contact or intravenous (IV) drug use. Baseline prothrombin time, activated partial thromboplastin time and factor VIII levels were 12 seconds (reference range 9.3–12.8), >120 seconds (reference range 22.9–34.5), and 2.9% (reference range 50–149) respectively. Inhibitor screening was negative; therefore, Bethesda assay was not indicated. Family history revealed a twin brother (alive) and four maternal uncles (deceased) with severe haemophilia A. Mutation analysis for the haemophilia A gene was not performed due to a limited testing facility.

Three days after clinical presentation, serological testing

¹Fatimid Foundation, Karachi, Pakistan; ²South City Hospital, Karachi, Pakistan; ³

⁵Fatimid Foundation, Karachi, Pakistan; ⁶Department of Surgery, The Aga Khan University Hospital, Karachi, Pakistan

Correspondence: Shabneez Hussain. e-mail: shabneez.haem@gmail.com

(electrochemiluminescence assay, Cobas e601) for hepatitis C (Anti-HCV) was reactive while hepatitis B surface antigen was non-reactive. HCV RNA (Genotype 3) was identified after two days and oral treatment of hepatitis C with Sofosbuvir (400 mg daily) and Ribavirin (800mg daily) was initiated immediately (Table I depicts the timeline of events).

Two months after the initiation of hepatitis C treatment, the patient developed pancytopenia with reticulocytopenia (0.7%). CBC revealed Hb 9.1 gm/dl, Hct 26.6 %, MCV 100.8 fl, MCH 34.5 pg, WBC $2.6 \times 10^9/L$, ANC $1.2 \times 10^9/L$, and platelet count $9 \times 10^9/L$. Bone marrow biopsy, performed after 45 days of onset of pancytopenia, showed severe aplasia with a cellularity ranging from 10 to 15%. Bone marrow was a moderately cellular specimen showing prominent erythroid and myeloid precursors with scanty megakaryocytes. Differential diagnosis for severe aplastic anaemia includes parvovirus B-19 and HIV infection. Parvovirus antigen and antibody tests were not performed due to its lack of availability in our centre while HIV 1/2 serology (electrochemiluminescence assay, Cobas e601), was reactive and HIV RNA was detected. CD4 count was 411 cells/ μl (21.12%, reference range 492-2014 cells/ μl) indicating the patient's immunocompromised state. Serum creatinine and liver transaminases were within the reference range. Our patient was treated with highly active antiretroviral therapy (HAART) by prescribing Efavirenz (600 mg), Lamivudine (300 mg), and Tenofovir (300 mg) while being monitored for resolution of pancytopenia with CBC every week.

After one month of treatment with HAART, he developed swelling and tenderness in the left thigh. He was treated with recombinant factor VIII concentrates due to clinical suspicion of haematoma. Lack of clinical improvement and onset of high-grade fever led to the suspicion of an

intramuscular abscess. Pus was aspirated and culture revealed a heavy growth of *Staphylococcus aureus*. He was treated with broad-spectrum antibiotics for one month. After incision and drainage, there was continuous bleeding from the wound site which showed severe necrosis with visibility of the underlying bone. He was under transfusion support (packed red cells and platelets) and was regularly infused with recombinant factor VIII concentrates to maintain a trough level of factor VIII at 40%. Daily dry dressing and slow wound debridement were performed under cover of recombinant factor VIII concentrates (10 IU/kg) for four months followed by alternate days for eight months (Figure 1). Wound healing was complete at one year.

After six months of oral hepatitis C treatment and HAART, HCV and HIV RNA were negative while pancytopenia persisted. The mean haemoglobin, white blood cell, absolute neutrophil and platelet counts were 7.7 gm/dl, $1.8 \times 10^9/L$, $0.5 \times 10^9/L$ and $17 \times 10^9/L$, respectively, during the initial six months of treatment with HAART. Trend of haemoglobin, platelet and white blood cell count during

Table: Timeline of events.

S. N.	Event	Date
1.	Clinical presentation with anaemia and thrombocytopenia	October 3, 2015
2.	Serological testing (electrochemiluminescence assay) for Hepatitis C and Hepatitis B	October 6, 2015
3.	Confirmatory test for hepatitis C by polymerase chain reaction	October 8, 2015
4.	Beginning of oral treatment for Hepatitis C	October 9, 2015
5.	Beginning of pancytopenia	November 27, 2015
6.	Bone marrow and trephine performed	January 12, 2016
7.	HIV serology (electrochemiluminescence assay) performed	January 14, 2016
8.	CD4 count performed	January 16, 2016
9.	Highly active anti-retroviral therapy (HAART) started	January 18, 2016
10.	Development of thigh swelling	February 2, 2016
11.	Incision & drainage of thigh swelling	February 19, 2016
12.	Repeat testing for hepatitis C and HIV by polymerase chain reaction	March 30, 2016
13.	Resolution of thigh wound	February 1, 2017
14.	Death due to septic shock	February 29, 2017

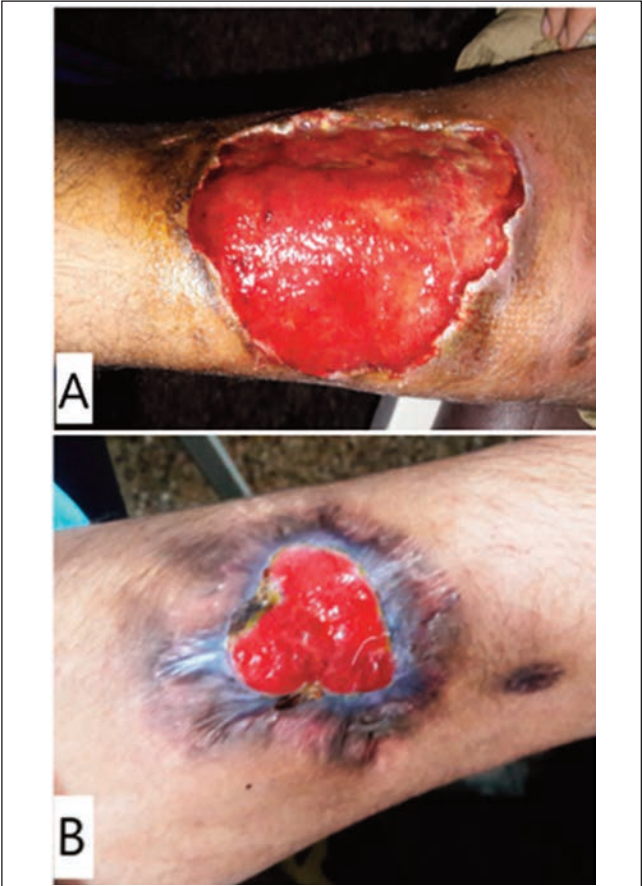
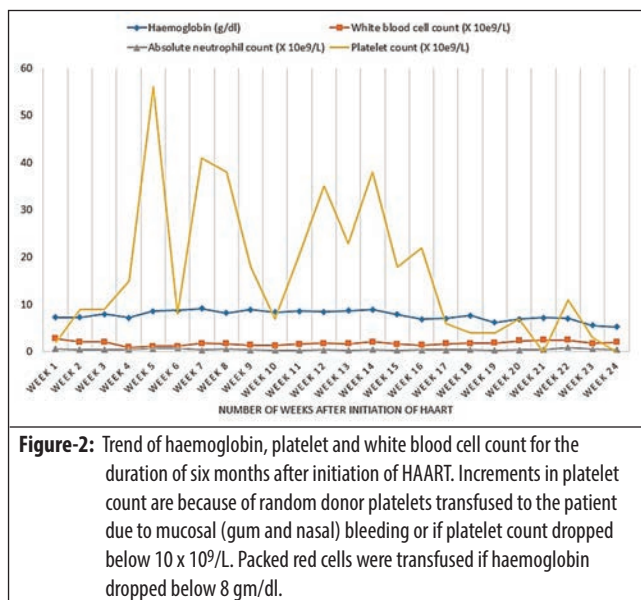


Figure-1: Wound on the anterior aspect of the left thigh in a haemophilia A patient showing granulation tissue at 8 (A) and 10 (B) months of regular dry dressing under cover of recombinant factor VIII concentrate (10 IU/kg).



six months after the initiation of HAART is shown in Figure 2.

Eighteen months after the initial clinical presentation, he developed septic arthritis and haemarthrosis of the left elbow and right knee joint. On admission, factor VIII level was 2.8% and bethesda assay was 1.2 BU/ml (reference range ≤ 0.6 BU/ml).⁵ Due to limited testing capabilities, inhibitors were not confirmed by half-life tests. The patient underwent an arthrotomy of the right knee and wound debridement of the left elbow under cover of recombinant factor VIIa. Post-surgery Bethesda assay was <1 BU/ml. Bleeding from the operated site stopped on 14th post-operative day. Joint aspirate and blood cultures for bacterial growth, acid-fast bacilli, and fungus were negative, while C reactive protein was persistently raised. Complete recovery of the elbow joint was documented; however, the knee joint remained affected. On 20th post-operative day, he developed bleeding per rectum, fever, petechial rash, and right leg swelling. He was advised above-knee amputation. However, the patient expired in February 2017 due to septic shock. Post mortem blood cultures revealed growth of *Klebsiella pneumonia* and *Acinetobacter* species.

Written informed consent was obtained from the patient's next-of-kin for publication of this case report.

Discussion

We report a case of moderate haemophilia A patient, who developed acquired aplastic anaemia preceded by HCV and HIV co-infection. Blood donors in Pakistan have a high prevalence of hepatitis C (4%) and B (3.3%) as compared to HIV (0.007%).⁶ In our setup, donor screening for HBV, HCV,

and HIV is performed by electro-chemiluminescence assay. Despite screening, there remains a substantial risk of viral transmission through blood transfusion due to low antibody titers secondary to an early phase of infection. The lack of a nucleic acid testing facility for screening of transfusion transmitted infections in haemophilia treatment centres further contributes to the risk of viral transmission. Our patient had a history of being treated with large amounts of cryoprecipitate and fresh frozen plasma since his diagnosis which exposed him to a risk of acquiring transfusion-transmitted infections.

The recommended therapy for severe aplastic anaemia in younger adults is matched, related donor haematopoietic stem cell transplant (HSCT) which is successful in up to 80% of patients, while immunosuppressive therapy using anti-thymocyte globulin and cyclosporin is successful in 50-70% of cases.⁷ In the absence of treatment, the mortality of severe aplastic anaemia is over 40% at two years after diagnosis.⁸ Ostronoff et al have reported successful treatment of aplastic anaemia in a haemophilia A patient due to unknown aetiology with HSCT.⁹ Another case treated successfully with HSCT was that of an adult with haemophilia and Burkitt-type acute lymphoblastic leukaemia.¹⁰ Hepatitis-associated aplastic anaemia in a boy with haemophilia B has been previously reported from our centre and immunosuppressive therapy was indicated but due to financial constraints, the patient was unable to be treated accordingly.¹¹

Although HSCT has proven to be successful in patients with severe aplastic anaemia, it is very challenging when severe aplastic anaemia is associated with HIV, due to the immunocompromised status of the patient. Positive outcomes have been documented in patients transplanted after a reduced-intensity conditioning regimen under combined anti-retroviral therapy; however, there is a high risk of drug interactions (between chemotherapy and HAART), graft failure, and rebound of HIV infection after transplant.^{12,13} It is also worth mentioning that immunosuppressive therapy is not indicated in patients who are immunocompromised.^{12,13} Due to significant financial constraints and high risk of procedure-related complications, HSCT was not considered as a treatment option for our patient. Another limitation is the delay in publication of this case report, considering that the patient expired in 2017 and the report is being published in 2022.

Conclusion

In Pakistan, haemophilia patients mainly belong to lower socioeconomic status which limits their access to treatment. The lack of access to curative therapy for aplastic anaemia underlines the need for truly universal access to

virally inactivated replacement therapy in patients with haemophilia where prevention is a better option than cure. The risk of transfusion-transmitted infections should be reduced by introducing nucleic acid testing in haemophilia treatment centres, especially in low middle-income countries where transfusion of cryoprecipitate and fresh frozen plasma is the main modality of treatment in haemophilia patients.

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