Case Report

SAGE Open Medical Case Reports

SAGE Open Medical Case Reports
Volume 8: 1–5

DOI: 10.1177/2050313X20901937
journals.sagepub.com/home/sco
SAGE

Hepatitis-associated aplastic anemia from workout supplement: Rare but potentially fatal entity

Sanjog Bastola[1,2], Ojbindra Kc[1,2], Sumesh Khanal[1] and Alexandra Halalau[1,2]

Abstract

Hepatitis-associated aplastic anemia (HAAA) is a rare clinical syndrome characterized by bone marrow failure 1–3 months after development of hepatitis. Untreated, hepatitis-associated aplastic anemia has poor outcome and the mainstay of treatment remains either bone marrow transplant or immunosuppressive therapy. A previously healthy 21-year-old man presented with a 1-week history of right upper quadrant pain and jaundice. Admission labs revealed mixed hyperbilirubinemia and elevated transaminases ranging in 2000s IU/dl. Extensive workup for etiologies of acute hepatitis including viruses, autoimmune, toxins etc. were negative. He admitted to taking "Dust V2," a workout supplement, for 4 months prior to the presentation. His liver function tests started to improve after conservative treatment. Two months after his discharge, he was found to have severe pancytopenia on routine labs. Bone marrow biopsy revealed hypocellular marrow consistent with aplastic anemia. Extensive workup for etiologies of aplastic anemia were negative. On literature review, none of the components of the supplement were found to cause aplastic anemia. A diagnosis of hepatitis-associated aplastic anemia was made as there was a lag time before development of anemia. His counts failed to improve despite treatment with filgrastim and he was referred for hematopoietic cell transplant.

Keywords

Hematology, gastroenterology/hepatology, aplastic anemia, hepatitis, workout supplement

Date received: 17 January 2019; accepted: 31 December 2019

Introduction

Severe aplastic anemia (AA) is defined as severe pancytopenia with at least two of the following: absolute neutrophil count of less than 500/mm^3, a platelet count of less than 20×10^3/mm^3, and reticulocyte count of less than 20×10^3/mm^3 in the presence of bone marrow cellularity of $<25\%$.[1] Underlying pathophysiology in AA is destruction of hematopoietic stem cells (HSCs), etiology of which in many cases remain unidentified. Most of these patients with AA appear to have a component of autoimmune destruction of HSC.[2–4] Other secondary causes for AA are viral infections, medications, radiation, and toxins. Hepatitis-associated aplastic anemia (HAAA) is one of the rare secondary causes of AA, especially in young adults that typically presents within 3 months of an acute episode of hepatitis. Hepatitis may be severe fulminant, self-limiting, or chronic.[4] In majority of these cases, the etiology of hepatitis is not identified and is thought to be due to an undetermined virus.[4] Overall prognosis of AA has improved in recent years due to increasing availability of HSC transplant, immunosuppressive therapy, and supportive care, with survival rates as high as 80%–90% compared with 10%–20% in the 1960s.[5,6] Prognosis is very similar for different etiologies of AA. Major factor that affects prognosis includes severity of pancytopenia, initial response to therapy, and patient's age. Untreated, 1-year mortality is 70%.[7]

Toxins including various dietary supplements and workout protein supplements are one of many etiologies of AA.

[1]Department of Internal Medicine, William Beaumont Hospital, Royal Oak, MI, USA
[2]Oakland University William Beaumont School of Medicine, Rochester, MI, USA

Corresponding Author:
Sanjog Bastola, Department of Internal Medicine, William Beaumont Hospital, 3601, W13 Mile Road, Royal Oak, MI 48073, USA.
Email: sanjogbastola@gmail.com

Table 1. Ingredients of workout supplement.

Beta alanine	L-Taurine	L-Carnitine-L-tartrate	Citrulline malate
N-acetyl-L-tyrosine	Betaine anhydrous	Agmatine sulfate	L-Norvaline
Di-caffeine malate	Caffeine anhydrous	Hordenine	*N*-methyltyramine
Stearoyl vanillylamide	Maltodextrin	Erythritol	Citric acid
Malic acid	Silicon dioxide		

Data are lacking to quantify the frequency of these adverse events associated with these supplements. Many of these dietary supplements contain a wide variety of undeclared active components and the nature of adverse event is unpredictable. Estimated 23,000 emergency visits are attributed to adverse events related to these supplements in the United States.[8] Manifestations vary widely ranging from cardiac manifestations like tachycardia and palpitation to fulminant hepatic failure and AA as in our patient.

Dietary supplements and workout supplements remain regulated through The Food and Drug Administration (FDA) in the United States. If a supplement is found to be unsafe, FDA can have manufacturer remove the product from the market. However, neither safety testing nor FDA approval is required before the marketing of dietary supplement.[8]

Table 2. Initial laboratory for acute hepatitis workup.

Laboratory	Value	Normal value
Ferritin	929 ng/mL	14–338 ng/mL
Iron	151 µg/dL	45–160 µg/dL
TIBC	428 µg/dL	228–417 µg/dL
Saturation (%)	35%	15%–55%
IgG	759 mg/dL	520–1560 mg/dL
IgA	80 mg/dL	88–374 mg/dL
IgM	38 mg/dL	47–206 mg/dL
Alpha 1 antitrypsin	183 mg/dL	100–240 mg/dL
AFP tumor marker	1.9 ng/dL	0.0–8.4 ng/dL
Ceruloplasmin	35 mg/dL	17–40 mg/dL
Ethanol level	$<$10 mg/dL	$<$10 mg/dL
Urine drug screen	Negative	Negative

TIBC: total iron binding capacity; AFP: alpha-fetoprotein.

Case presentation

A 21-year-old man with no significant past medical history presented to the emergency department with right upper quadrant pain and jaundice for a week. He gave history of dark urine and pale stool of same duration. He also admitted to fatigue, poor appetite, and nausea but denied any fever, chills, diarrhea, or any weight changes. He denied any confusion, mental status changes, any hematemesis, hematochezia, or melena. He denied any recent travel outside the United States or high-risk sexual behavior. He denied any history of incarceration or tattoos. He denied history of tobacco use or any recreational drug abuse. He gave history of drinking one to two drinks of alcohol per week and his last drink was 2 weeks prior to presentation. He denied taking any over the counter medication or herbal supplements. However, he admitted to taking "Dust V2," a workout protein supplement for 4 months (ingredients on Table 1). He denied family history of any liver disease.

On examination, he had diffuse icterus and tender hepatomegaly. No clinical stigmata of chronic liver disease was identified. The laboratory evaluation revealed aspartate aminotransferase (AST) of 1224 IU/dL, alanine transaminase (ALT) of 2908 IU/dL, total bilirubin of 9.4 mg/dL, and alkaline phosphatase of 86 IU/dL. Complete blood count and prothrombin time (PT) were normal at the time of presentation. Initial lab workup for acute hepatitis was unremarkable (Table 2). The baseline serologic workup is shown in Table 3 which ruled out any infectious, autoimmune, or metabolic causes of his liver disease.

Abdominal magnetic resonance imaging (MRI) and magnetic resonance cholangiopancreatography (MRCP) showed hepatomegaly but no any masses, biliary obstruction or portal vein obstruction. He underwent a liver biopsy for further confirmation which revealed lobular inflammation with predominant lymphocytes consistent with drug-induced hepatitis. Trichrome stain demonstrated mild portal fibrosis with pericellular fibrosis in areas of hepatocyte dropout (Figures 1 and 2). Special stains for iron and copper (iron stain and Rhodanine stain) were both negative. A special stain for cytoplasmic inclusions (PAS stain with diastase) was also negative. He was managed conservatively with supportive therapy and his liver function test (LFT) started to trend down. He felt symptomatically better and was discharged home.

Two months after initial presentation, he was found to have severe pancytopenia on routine blood counts. Labs revealed white blood cell (WBC) count of 1.3 bil/L with neutrophils 0.8 bil/L. His hemoglobin was 8.4 g/dL and platelet count was 19 bil/L. His AST was 546 IU/L, ALT was 1811 IU/L, and total bilirubin was 6.4. Peripheral smear showed severe neutropenia with thrombocytopenia. Bone marrow biopsy revealed marked hypocellularity ($<$5%) with stromal damage (Figure 3). No blasts and no morphologic evidence of malignancy were identified. Flow cytometry was negative for malignancy. Cytogenetic study showed normal karyotype. Bone marrow biopsy was negative for germline mutation and Paroxysmal Nocturnal Hemoglobinuria(PNH) clone. Infectious workup was negative. On extensive literature review, none of the

Table 3. Initial autoimmune and virology for acute hepatitis workup.

Laboratory	Value
Antinuclear antibodies	Negative
Antimitochondrial antibodies	Negative
Smooth muscle antibody	Negative
Liver kidney microsomal antibody	Negative
Anti-Smith antibody	Negative
Hemochromatosis mutation	Negative
HIV 1 and 2 antibodies	Non-reactive
CMV IgG antibody	Negative
CMV IgM antibody	Negative
EBV IgG antibody	Positive
EBV IgM antibody negative	Negative
Hepatitis A IgM	Non-reactive
Hepatitis B core IgG	Non-reactive
Hepatitis B surface IgG	Non-reactive
Hepatitis B surface antigen	Non-reactive
Hepatitis C antibodies	Non-reactive
Repeated at later date	Non-reactive
Herpes 1 IgG antibody	Negative
Herpes 2 IgG antibody	Negative
HSV IgM antibody	Negative
HSV PCR qualitative	Not detected
Parvovirus B19 IgG and IgM antibody	Negative
Hepatitis E IgG and IgM	Negative

CMV: cytomegalovirus; EBV: Epstein–Barr virus; HSV: herpes simplex virus; PCR: polymerase chain reaction.

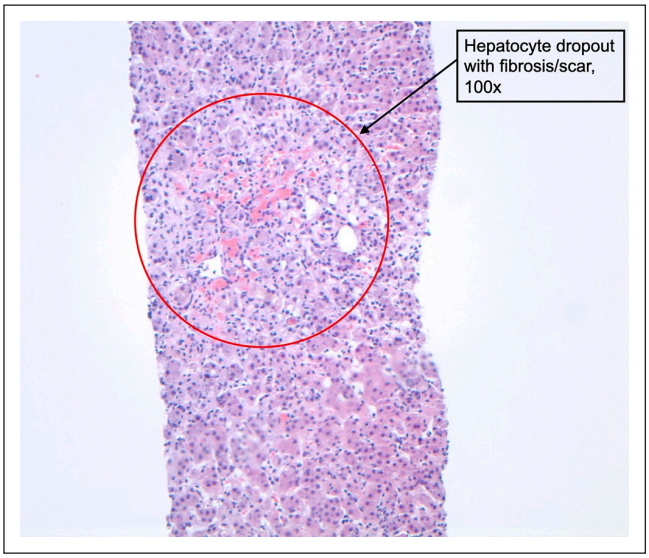

Figure 1. Pericellular fibrosis with areas of hepatocyte drop out in liver biopsy.

components of the workout supplement were found to cause AA or hepatitis.[9] A diagnosis of HAAA was made as there was a lag time of months before development of anemia and extensive workup for other etiology for aplastic was negative. His

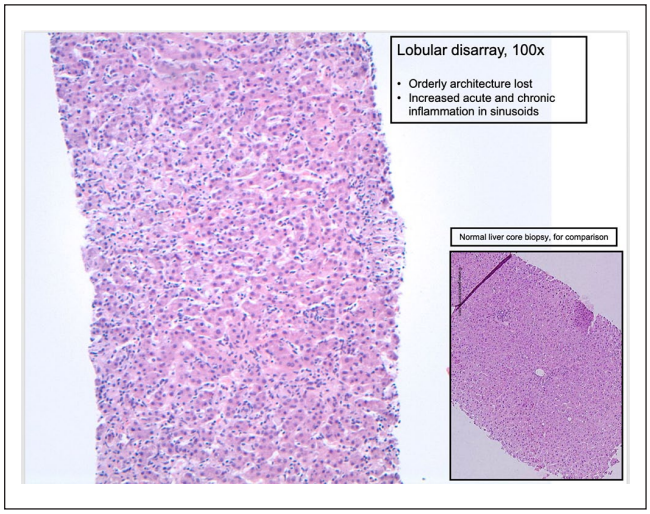

Figure 2. Lobular inflammation with predominant lymphocytes in liver biopsy.

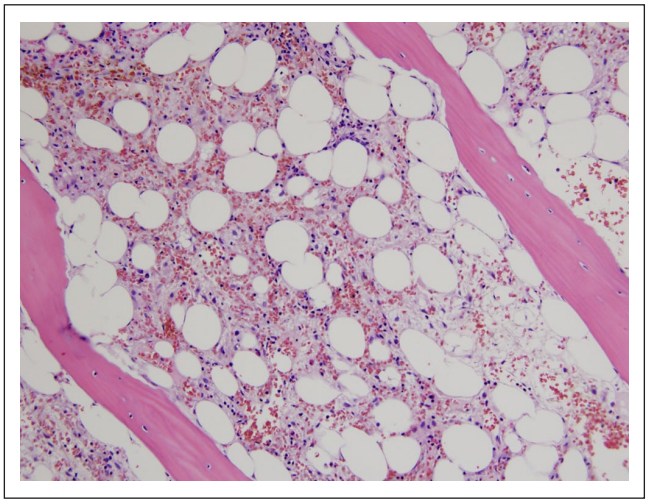

Figure 3. Trilineage hypoplasia in bone marrow biopsy.

counts failed to improve despite treatment with filgrastim and he was referred for hematopoietic cell transplant (HCT). He underwent 4/6 human leukocyte antigen (HLA)-matched related donor HCT with conditioning regimen of thymoglobulin, fludarabine, and cyclophosphamide. His LFTs remained stable post conditioning regimen. His post-transplant course was complicated by cutaneous graft versus host disease (GVHD) and remains on tacrolimus. His counts have recovered, LFT normalized and he continues to do well 7 months post-transplant (Table 4).

Discussion

Hepatitis is fairly common problem in primary care setting and every clinician should be aware of the potential complications including AA and ensure proper follow-up. HAAA as

Table 4. Lab test flow chart.

	Day 0	Day 7	Day 70		Day 90		Day 360	Day 450
WBC	4.8	4.3	0.3	Filgrastim on day 65	0.1	HCT on day 300	3.4	5.2
Hemoglobin	10.8	10	8.8		5.1		8.7	10.9
Platelets	197	232	4		<1		173	187
Neutrophils	2.7	2.4	<0.1		<0.1		2	3.2
ALP	86	67	101		59		83	98
AST	1224	988	438		19		38	35
ALT	2908	1783	1645		21		72	94
Total bilirubin	9.4	18.3	2.6		4.9		0.4	0.3

HCT: hematopoietic cell transplant; WBC: white blood count × 1000/mm^3; ALP: alkaline phosphatase (IU/dL); AST: aspartate aminotransferase (IU/dL); ALT: alanine aminotransferase (IU/dL).

a secondary cause of AA has been reported in 2%–5% of cases in Western literature.[3] Typically it presents in young adults and children, usually male with onset of pancytopenia 1–3 months after episode of acute hepatitis. Our patient had onset within 2 months of initial hepatitis and was continuing to have mild hepatitis at the onset on AA. The etiology of hepatitis is either idiopathic in most cases or due to any of the hepatitis viruses, parvovirus B19, cytomegalovirus, Epstein–Barr virus, or toxin induced as in our case. A possible hepatotropic virus was identified in less than 6% patients with HAAA in two studies.[10,11] Our case is unique in that describes AA that occurred after toxin-induced hepatitis from workout supplement. Most of the cases has been described after viral hepatitis or are idiopathic. We were able to find only one such case report where the hepatitis was caused by toxin.[12] Our case sheds light in the outcome after HCT in toxin-induced HAAA. Hepatotoxicity in the form of intrabiliary cholestasis and hepatitis associated with workout supplements has been widely reported but they are not specifically considered myelotoxic.[12] Time interval of 1–3 months suggests the initial target of the immunological response is the liver. This theory is supported by improvement in LFTs to immunosuppressives administered for the bone marrow aplasia.[2,3] It has been postulated that antigens induce CD-8 lymphocyte activation and lead to apoptotic destruction of hematopoietic cells.[4] In addition, interferon-gamma is found to be a marrow suppressing cytokine and is secreted by activated T cells. Hepatitis may be of any severity ranging from fulminant hepatitis to asymptomatic mild hepatitis. Initial acute hepatitis may resolve or patients may continue to have mild hepatitis as in our patient in up to 40% cases.[13]

Typical presentation includes pallor, fatigue, petechial rashes, and infections from pancytopenia. These patients are susceptible for bacterial or invasive fungal infections which are common causes for death. Diagnosis is made by preceding history of hepatitis and pancytopenia in complete blood count (CBC). Bone marrow biopsy typically shows profound hypocellularity with morphologically normal residual hematopoietic cells and absence of malignant infiltration and fibrosis.[4]

Treatment includes supportive therapy and definitive therapy for AA.[12] Two major treatment options for treating HAAA are bone marrow transplantation (BMT) and immunosuppressive therapy. Hendren et al. reported resolution of acute hepatitis B–associated AA with antiviral therapy. Patients with severe neutropenia are susceptible to serious infections and may need antibiotics and antifungals. BMT is preferred over immune suppressive therapy if HLA-matched sibling donor is available. In a study, mean survival in 163 patients was 82% after BMT.[4] The survival rate after BMT in HAAA is similar to that for patients without HAAA. Patients who are treated with immunosuppressive therapy are at increased risk of acute myeloid leukemia (AML) or myelodisplastic syndrome (MDS) in later life and need lifelong clinical monitoring.

In conclusion, HAAA is relatively rare clinical entity where initial hepatitis leads to subsequent AA due to immunologic mechanisms. Inciting event for initial hepatitis may be any of the viruses or in rare occasion drug induced as in our case. Most of the cases occur in young adults and prompt diagnosis and treatment is crucial as untreated prognosis is poor. Our patient had HLA-matched sibling and was able to get HCT with good outcome.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

Our institution does not require ethical approval for reporting individual cases or case series.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Informed consent

Written consent was obtained from the patient(s) for their anonymized information to be published in this article.

ORCID iD

Sanjog Bastola https://orcid.org/0000-0003-4819-0985

References

1. Davies JK and Guinan EC. An update on the management of severe idiopathic aplastic anaemia in children. *Br J Haematol* 2007; 136(4): 549–564.
2. Scheinberg P and Chen J. Aplastic anemia: what have we learned from animal models and from the clinic. *Semin Hematol* 2013; 50(2): 156–164.
3. Brown KE, Tisdale J, Barrett AJ, et al. Hepatitis-associated aplastic anaemia. *N Engl J Med* 1997; 336(15): 1059–1064.
4. Gonzalez-Casas R, Garcia-Buey L, Jones EA, et al. Systematic review: hepatitis-associated aplastic anaemia-a syndrome associated with abnormal immunological function. *Aliment Pharmacol Ther* 2009; 30(5): 436–443.
5. Höchsmann B, Moicean A, Risitano A, et al. Supportive care in severe and very severe aplastic anemia. *Bone Marrow Transplant* 2013; 48(2): 168–173.
6. Scheinberg P. Aplastic anemia: therapeutic updates in immunosuppression and transplantation. *Hematology Am Soc Hematol Educ Program* 2012; 2012: 292–300.
7. Young NS. Aplastic anaemia. *Lancet* 1995; 346: 228–232.
8. Geller A, Shehab N, Weidle N, et al. Emergency department visits for adverse events related to dietary supplements. *N Engl J Med* 2015; 373: 1531–1540.
9. Biesterbos JWH, Sijm DTHM, van Dam R, et al. A health risk for consumers: the presence of adulterated food supplements in the Netherlands. *Food Addit Contam Part A Chem Anal Control Expo Risk Assess* 2019; 36(9): 1273–1288.
10. Patel KR, Bertuch A, Sasa GS, et al. Features of hepatitis in hepatitis-associated aplastic anemia: clinical and histopathologic study. *J Pediatr Gastroenterol Nutr* 2017; 64(1): e7–e12.
11. Locasciulli A, Bacigalupo A, Bruno B, et al. Hepatitis-associated aplastic anaemia: epidemiology and treatment results obtained in Europe. A report of the eBMt aplastic anaemia working party. *Br J Haematol* 2010; 149(6): 890–895.
12. Qureshi K. Severe aplastic anemia following acute hepatitis from toxic liver injury: literature review and case report of a successful outcome. *Case Reports Hepatol* 2014; 2014: 216570, https://www.hindawi.com/journals/crihep/2014/216570/
13. Safadi R, Or R, Ilan Y, et al. Lack of known hepatitis virus in hepatitis-associated aplastic anemia and outcome after bone marrow transplantation. *Bone Marrow Transplant* 2001; 27(2): 183–190.