CASE REPORT

Resolution of acute hepatitis B-associated aplastic anaemia with antiviral therapy

Nicholas Hendren,¹ Joseph Moore,¹ Sandra Hofmann,² Siyareh Rambally²¹Department of Internal Medicine, University of Texas Southwestern, Dallas, Texas, USA²Division of Hematology and Oncology, Internal Medicine, University of Texas Southwestern Medical Center, Dallas, Texas, USA

Correspondence to

Dr Nicholas Hendren,
nicholas.hendren@phhs.org

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SUMMARY

A previously healthy 44-year-old woman presented with 3 days of worsening petechial rash, epistaxis and fatigue. Admission labs revealed pancytopenia, low reticulocyte index and elevated liver enzymes. Bone marrow biopsy demonstrated a profoundly hypocellular bone marrow without dysplasia and additional testing demonstrated an acute hepatitis B infection. In the context of an acute hepatitis B infection, elevated liver enzymes and aplastic anaemia, our patient was diagnosed with severe hepatitis-associated aplastic anaemia due to an acute hepatitis B infection. She was initiated on antiviral therapy with tenofovir and briefly received immunosuppressive therapy with a robust sustained improvement in her blood counts. Acute hepatitis B-associated aplastic anaemia is an exceptionally rare presentation of aplastic anaemia. We present acute hepatitis B-associated aplastic anaemia that resolved with antiviral therapy, which to our knowledge is the second such case reported in the literature and the first using tenofovir.

BACKGROUND

Aplastic anaemia is a rare condition defined by pancytopenia with hypocellularity (<30%) of the bone marrow and the absence of myelodysplasia.¹ The pathophysiology of the impairment in haematopoiesis is thought to be secondary to immune-mediated destruction of pluripotent stem cells.^{2,3} Cases may be idiopathic or secondary to an underlying condition such as pregnancy, viral infections, medications, radiotherapy or toxins.⁴ Hepatitis-associated aplastic anaemia (HAA) is a rare secondary cause of aplastic anaemia that typically presents within 3 months of an acute episode of hepatitis.⁴ Although the aetiology of HAA is often idiopathic, rarely viral and autoimmune causes are identified.⁴ We present a rare case of acute hepatitis B-associated aplastic anaemia that resolved with treatment of the underlying viral infection. To our knowledge, this is the second such case reported in the literature and the first case treated with tenofovir supporting a rare presumed causal relationship between hepatitis B and aplastic anaemia.⁵

CASE PRESENTATION

A previously healthy 44-year-old woman presented with 3 days of malaise, fatigue, headache, myalgias, petechial rash and epistaxis. Her review of symptoms was otherwise unremarkable. There were no new medications, including vitamins or herbal

supplements. She had one tattoo obtained 8 years prior to admission at a licensed tattoo parlour. There was no history of blood transfusions, blood exposures, needle stick injuries or toxin exposures. She denied any alcohol or illicit drug use. She reported a new heterosexual relationship started within the last 2 months, involving unprotected intercourse. On examination, vital signs were normal. Skin exam was notable for non-blanching, non-palpable petechial rash involving the palate, torso and extremities. The remainder of the physical exam, including lymph node and abdominal exam, was unremarkable.

INVESTIGATIONS

Admission laboratory studies revealed pancytopenia (white cell count $2.2 \times 10^9/L$ (normal $4-11 \times 10^9/L$), absolute neutrophil count (ANC) $1.6 \times 10^9/L$ (normal $1.5-7.5 \times 10^9/L$), haemoglobin 10.2 g/dL (normal 13.2–16.9 g/dL), platelets <5 (normal $160-383 \times 10^9/L$) and reticulocytopenia (absolute reticulocyte count <10 (normal $42-123 \times 10^9/L$)). Peripheral blood smear showed the absence of platelets, without any overt signs of dysplasia, leucoerythroblastic features or immature circulating cells (figure 1). Hepatic enzymes were elevated and consistent with a hepatocellular injury pattern (aspartate transaminase (AST) 346 U/L (normal range 10–50 U/L), alanine transaminase (ALT) 794 U/L (normal 10–50 U/L), alkaline phosphatase 176 U/L (normal 40–129 U/L)) with normal total bilirubin. Workup of the transaminitis revealed a positive hepatitis B surface antigen. Additional testing revealed a positive hepatitis B core IgM, positive hepatitis B core IgG, negative hepatitis B surface antibody, positive hepatitis Be antigen and a negative hepatitis Be antibody consistent with acute hepatitis B infection. Hepatitis B PCR returned with >170 million IU/mL. Additional infectious workup was negative for HIV PCR, cytomegalovirus (CMV) PCR, parvovirus B19 PCR, Epstein-Barr virus (EBV) IgM, hepatitis C antibody and hepatitis A IgM. A liver ultrasound was unremarkable. Liver function tests and complete blood counts obtained 14 months prior to admission were normal. Hepatitis B surface antigen was negative 29 months prior to presentation.

DIFFERENTIAL DIAGNOSIS

Given the pancytopenia with an inappropriately low absolute reticulocyte count, we were concerned for primary bone marrow failure. The absence of

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Figure 1 Peripheral blood smear, Wright's stain, 20 $\times$. The peripheral blood shows normocytic, normochromic anaemia. The neutrophils do not exhibit nuclear dysplastic features. The platelets are decreased in number.

leucoerythroblastic features and immature cells on the peripheral blood smear made infiltration of the bone marrow and acute leukaemia less likely. Myelodysplastic syndrome (MDS) was on the differential diagnosis, but there were no overt dysplastic features on the peripheral blood smear and she had no risk factors for the development of early onset MDS. The bland smear findings and the absence of reticulocytes were concerning for aplastic anaemia.

Alternative diagnoses such as, aplastic crisis, nutritional deficiencies, HIV and parvovirus were considered. A bone marrow biopsy obtained on day 2 of admission demonstrated a profoundly hypocellular bone marrow (<5% cellularity) with no signs of dysplasia or increase in blast percentage (figures 2 and 3). Conventional cytogenetics on the bone marrow aspirate revealed a normal karyotype. MDS fluorescent in situ hybridisation panel was negative. Peripheral blood flow cytometry was negative for a paroxysmal nocturnal haemoglobinuria clone.

Figure 2 Bone marrow aspirate smear, Wright's stain. The aspirate smear shows a hypocellular particle of marrow with rare maturing marrow elements (original magnification 10 $\times$). The majority of aspirate was composed of mature neutrophils and lymphocytes with rare maturing erythroids or megakaryocytes seen (inset, original magnification 20 $\times$).

Figure 3 Bone marrow core biopsy, H&E. The megakaryocytes, erythroids and myeloid lineages are decreased to virtually absent on the core biopsy (original magnification 20 $\times$). The bone marrow cellularity is approximately 5% cellular which is hypocellular for age in this patient (inset, original magnification 2 $\times$).

TREATMENT

In the context of acute hepatitis B infection, elevated liver enzymes and aplastic anaemia, our patient was diagnosed with severe hepatitis-associated aplastic anaemia due to acute hepatitis B infection. Given the acute hepatitis B infection and the presumed need to initiate immunosuppressive therapy, she was started on tenofovir 300 mg once daily on the second day of admission and liver function tests normalised within 2 weeks (figure 4A). By the ninth day of admission, she had developed agranulocytosis with ANC <0.1 $\times 10^9/L$ and further decline in haemoglobin to <8 g/dL (figure 4B and C).

Due to her persistent pancytopenia and hypocellular bone marrow, she was initiated on immunosuppressive therapy (IST) with horse antithymocyte globulin (ATG) and ciclosporine on the 12th day of admission. Even before the 4 day infusion of ATG was complete, the total WBC, ANC and platelets had normalised with a significant improvement in her haemoglobin (figure 4B and C). The rapid improvement in haematopoiesis was inconsistent with an effect of IST, which usually requires 1–3 months for efficacy in aplastic anaemia.⁶ On chart review, her WBC and ANC subtly began to increase the day prior to

Figure 4 (A) Time course of AST, ALT and medical therapy from the date of admission. (B) Time course of WBC, ANC and medical therapy from the date of admission. (C) Time course of haemoglobin, platelet count and medical therapy from the date of admission. ALT, alanine transaminase; ANC, absolute neutrophil count; AST, aspartate transaminase; ATG, antithymocyte globulin; CSA, ciclosporin; WBC, white blood cell.

IST and her platelet count dramatically increased to $115 \times 10^9/L$ with antiviral therapy alone (figure 4B). Her hepatitis B virus DNA decreased from >170 million copies to 201 239 copies/mL after 1 month of therapy with tenofovir. Thus, the recovery of her counts was attributed to control of the hepatitis B infection with tenofovir rather than IST.

OUTCOME AND FOLLOW-UP

After a risk and benefit discussion with the patient, ciclosporin was rapidly tapered off over the next 2 months and she continues to have normal blood counts 4 months after her initial presentation. The patient discontinued tenofovir for approximately 3 weeks after the ciclosporin was tapered off and presented again with fatigue, nausea, pruritus and transaminitis. Interestingly, her blood counts remained normal and acute hepatitis responded to reinitiation of tenofovir.

DISCUSSION

HAA is a rare variant of aplastic anaemia that occurs after an episode of acute hepatitis and is estimated to cause 2%–5% of all cases of aplastic anaemia in the western hemisphere.^{1 7} Our patient met diagnostic criteria for severe aplastic anaemia, given the bone marrow cellularity <30%, ANC<500, platelet count < $20 \times 10^9/L$ and reticulocyte count <60 000/ μL . The aplastic anaemia was considered to be secondary to acute hepatitis B infection given the timing of her presentation. The presumed cause of hepatitis is largely unknown as the majority of patients with HAA test negative for hepatotropic viruses.^{8 9} Pancytopenia usually occurs within 2–3 months of the acute hepatitis, with some cases presenting within 1 week as our patient did.^{10 11} Immunologically mediated damage to the liver is a theory, supported by the response in liver function tests to immunosuppression administered for the bone marrow aplasia.¹¹ Alternatively, rare sporadic case reports have suggested associations between aplastic anaemia with parvovirus B19, human herpes virus-6, cytomegalovirus, EBV and hepatitis viruses.^{4 7}

A possible hepatotropic virus was identified in <6% of patients with HAA in two studies involving 214 and 36 patients.^{7 8} Hepatitis B-associated aplastic anaemia is an exceptionally rare presentation of aplastic anaemia. We are aware of six cases of acute hepatitis B-associated aplastic anaemia (published from 1975 to 2002); all except two cases occurred prior to the availability of hepatitis B antiviral medications.^{5 12–16} Bozkaya *et al* described a patient with hepatitis B-associated aplastic anaemia with a partial response to immunosuppressive therapy; however, after immunosuppressive therapy was withdrawn, the patient experienced recurrent acute hepatitis and bone marrow failure.⁵ The patient subsequently had a full remission of severe aplastic anaemia and resolution of hepatitis with lamivudine treatment.⁵

We attribute the haematopoietic response in our patient to tenofovir as opposed to the IST, given the robust response in platelet count prior to initiation of IST and the atypical rapid recovery of other cell lines within days of ATG/ciclosporin initiation. Given the clinical rarity of the condition and lack of available literature for acute hepatitis B-associated aplastic anaemia, we were unable to anticipate that she would not require IST. Fortunately, the IST does not seem to have had an adverse effect on her clinical course.

We believe that this case demonstrates a causal relationship between the hepatitis B infection and secondary aplastic anaemia, given resolution of both with antiviral therapy. The pathophysiology may be related to the expansion of cytotoxic T lymphocytes as a result of the hepatotropic virus, resulting in increased

production of myelosuppressive cytokines, interferon gamma and tumour necrosis factor alpha and ultimately apoptosis of haematopoietic precursors through the FAS receptor pathway.^{3 4} It is notable that our patient did not experience significant cytopenias during the brief 3–4 week period that she was off tenofovir, despite a flare in the acute hepatitis B infection and mild decrease in ANC and WBC. It is plausible that the recent immunosuppression with ATG/ciclosporin blunted the cytotoxic T cell response that may be necessary for the underlying marrow aplasia to develop.

We present the second case of hepatitis B-associated aplastic anaemia that resolved with antiviral therapy with sustained remission. This is an important observation as it supports the causal relationship between the entities of infectious hepatitis and marrow aplasia and is potentially practice changing as the risks of immunosuppression may be avoided. It is reasonable to question if she had temporary marrow suppression versus true hepatitis-associated aplastic anaemia. However, on literature review, we were unable to find any cases of myelosuppression with acute hepatitis B infection and she met diagnostic criteria for HAA. In sum, we believe this is the second described case of acute hepatitis B-associated aplastic anaemia treated with an antiviral medication for hepatitis B that resulted in resolution of hepatitis-associated aplastic anaemia.

Learning points

- ▶ Acute hepatitis B is a rare cause of hepatitis-associated aplastic anaemia.
- ▶ Patients diagnosed with aplastic anaemia should have a thorough workup for secondary aetiologies, which may affect management decisions.
- ▶ Hepatitis-associated aplastic anaemia due to acute hepatitis B infection may be sufficiently treated with antiviral therapy.

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REFERENCES

- 1 Rovó A, Tichelli A, Dufour C, *et al*. Diagnosis of acquired aplastic anemia. *Bone Marrow Transplant* 2013;48:162–7.
- 2 Antonello VS, Zalttron VF, Vial M, *et al*. Oropharyngeal histoplasmosis: report of eleven cases and review of the literature. *Rev Soc Bras Med Trop* 2011;44:26–9.
- 3 Young NS, Maciejewski J. The pathophysiology of acquired aplastic anemia. *N Engl J Med* 1997;336:1365–72.
- 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;30:436–43.
- 5 Bozkaya H, Yurdaydin C, Törüner M, *et al*. Remission of severe aplastic anemia associated with hepatitis B virus infection after viral clearance: potential role of lamivudine. *Dig Dis Sci* 2002;47:1782–5.
- 6 Frickhofen N, Kaltwasser JP, Schrezenmeier H, *et al*. Treatment of aplastic anemia with antilymphocyte globulin and methylprednisolone with or without ciclosporine. The German Aplastic Anemia Study Group. *N Engl J Med* 1991;324:1297–304.

- 7 Patel KR, Bertuch A, Sasa GS, *et al.* Features of hepatitis in hepatitis-associated splastic snemia: clinical and histopathologic study. *J Pediatr Gastroenterol Nutr* 2017;64:e7–e12.
- 8 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;149:890–5.
- 9 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;27:183–90.
- 10 Rauff B, Idrees M, Shah SA, *et al.* Hepatitis associated aplastic anemia: a review. *Viral J* 2011;8:87.
- 11 Brown KE, Tisdale J, Barrett AJ, *et al.* Hepatitis-associated aplastic anemia. *N Engl J Med* 1997;336:1059–64.
- 12 Adachi Y, Yasui H, Yuasa H, *et al.* Hepatitis B virus-associated aplastic anemia followed by myelodysplastic syndrome. *Am J Med* 2002;112:330–2.
- 13 Chong RS, Ng HS, Ong YY, *et al.* A case of aplastic anaemia associated with fulminant hepatitis B. *Singapore Med J* 1990;31:75–7.
- 14 McSweeney PA, Carter JM, Green GJ, *et al.* Fatal aplastic anemia associated with hepatitis B viral infection. *Am J Med* 1988;85:255–6.
- 15 Casciato DA, Klein CA, Kaplowitz N, *et al.* Aplastic anemia associated with type B viral hepatitis. *Arch Intern Med* 1978;138:1557–8.
- 16 Nakamura S, Sato T, Maeda T, *et al.* Viral hepatitis B and aplastic anemia. *Tohoku J Exp Med* 1975;116:101–2.

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