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CASE REPORT

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Recurrent idiopathic acute hepatitis-associated aplastic anemia/pancytopenia fourteen years after initial episode

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ABSTRACT

Aplastic anemia following viral hepatitis is a condition well recognized in the medical literature. Although hepatitis-associated aplastic anemia is an uncommon syndrome, there are several reports in the literature describing such cases. In these reports, aplastic anemia generally occurs following a viral infection, including parvovirus B19, but may also be idiopathic. The etiology of both the hepatic injury and the bone marrow failure is speculated to be immune-mediated. We report a patient who suffered acute idiopathic hepatitis and severe pancytopenia fourteen years after a similar episode in childhood. This is only the second case report of acute hepatitis in association with bone marrow failure and aplastic anemia in childhood with sudden recurrence many years later in adulthood.

Key words. Acute hepatitis. Aplastic anemia. Pancytopenia. Recurrent.

INTRODUCTION

Hepatitis-associated aplastic anemia (HAA) is a variant of aplastic anemia (AA), in which hepatitis precedes AA by weeks or months.[1] HAA most often affects young men, and occurs in 2-5% of cases of aplastic anemia in the West and 4-10% of cases in the Far East.[2,3] The underling pathological mechanism of AA is thought to be immune-mediated and this condition can be potentially fatal if not treated.[4] The treatment of HAA includes immunosuppressive therapy and haematological stem cell transplant (HCT).[4,5] The reported response rate to treatment ranges between 70-82%.[4-6]

CASE REPORT

A 20-year-old Caucasian man, born in rural British Columbia, Canada, was previously diagnosed with acute hepatitis-associated aplastic anemia at the age of seven years. The etiology of his hepatitis was not identified and he recovered from his hepatitis and aplastic anemia following immunosuppressant therapy with cyclosporine, prednisone and antithymocyte globulin, and fortunately did not require a bone marrow transplant. The medical history was unremarkable until age 20, when he presented again with acute hepatitis. The blood test results showed an alanine transaminase (ALT) level 2,500 U/L (normal <55 IU/L), aspartate transaminase (AST) 2,400 U/L (normal <38 IU/L), alkaline phosphatise (ALP) 127 U/L (normal <105 IU/L), total bilirubin 559 μmol/L (normal <20 μmol/L) and direct bilirubin 396 μmol/L. This was preceded by a skin rash and was associated with severe pancytopenia. The nadir hematologic profile at the time of presentation included: hemoglobin (Hb) of 63 g/L, a white cell count (WBC) of 1.2 x10^6/L and platelets of 10 x10^6/L.

Investigations for the etiology of acute hepatitis were negative (serology for hepatitis A, hepatitis B, hepatitis C, hepatitis E, Epstein-Barr virus, cytomegalovirus, autoimmune liver disease markers including antinuclear/antimitochondrial antibodies and anti-tissue transglutaminase and normal serum ceruloplasmin). The patient had no travel history and was not taking any prescription nor herbal medications. An abdominal ultrasound revealed a moderately enlarged spleen but no evidence of ascites nor hepatic vein thrombosis. A transjugular liver

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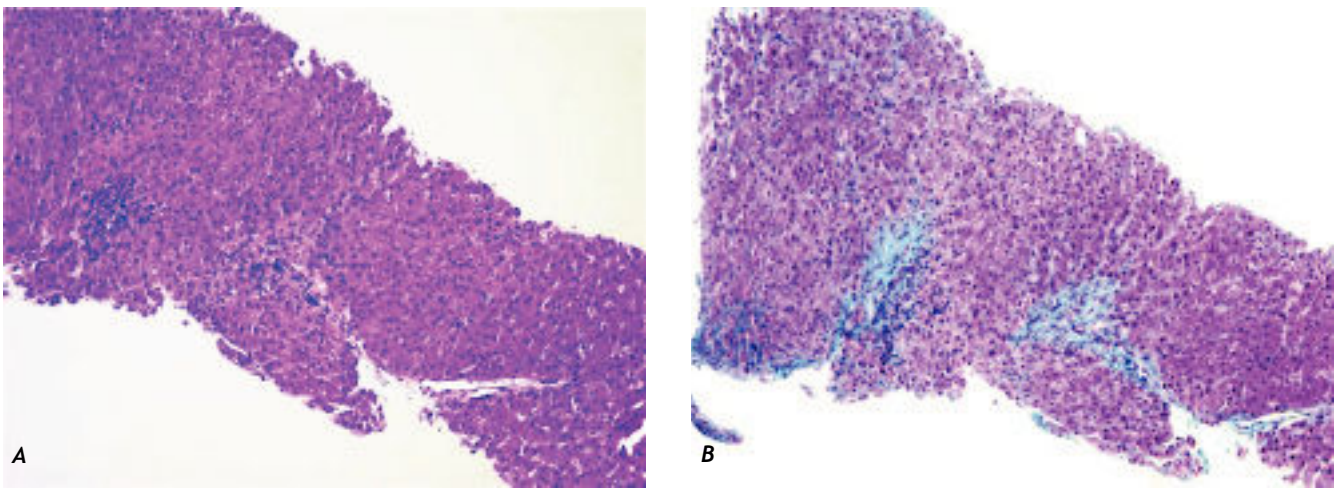

Figure 1. *Core liver biopsy, reveal mild fibrosis (trichrome stain in right sided figure with portal-based fibrosis in blue) and non-specific architectural distortion (H and E stain in left sided figure).*

biopsy revealed architectural distortion with mild fibrosis but was non-specific with respect to etiology (Figure 1). A bone marrow biopsy revealed a hypocellular marrow with decrease granulopoiesis and markedly reduced megakaryocytes.

The patient was managed conservatively with respect to liver disease and his liver biochemistry normalized within two months. His pancytopenia persisted despite normalization of his liver biochemistry and he received induction immunosuppresion consisting of antithymocyte globulin (ATG) and maintenance cyclosporine. Although he has been investigated for a possible allogenic stem cell transplant, at last follow-up, 4.5 months post-ATG and 10 months post-presentation, his leukocyte counts was 2.8 x 10^6/L, haemoglobin 113 g/L and platelet count 26 x10^6/L. The etiology of his disease remains idiopathic.

DISCUSSION

In a large number of reported cases of HAA the etiology was idiopathic, although it is presumed to be viral. In this current case, our patient had recurrent acute hepatitis with aplastic anemia in the first episode during childhood and severe pancytopenia with hypocellular bone marrow in the second episode, many years later in adulthood. The etiology was not identified in either episode. Parvovirus B19 is known to be one of the viral causes of HAA,[4,7] but it was not detected in this case.

The mechanism of AA is thought to be immune-mediated.[8] Several studies have reported an association between HAA and auto-activation of CD8 cells, which may be cytotoxic to myelopoietic cells in the bone marrow.[8] It is thought that viruses induce the activation of CD8 cells and thus ultimately lead to bone marrow suppression.[8]

Immunosuppressive therapy (IST) appears to act by reducing the circulating cytotoxic T cells and the response rate ranges between 70-80%.[5,6,9] Hematopoietic cell transplant (HCT) had been evaluated in the management of HAA and the survival rate of patients who undergo successful HCT is estimated to be 82% at 5 years.[10,11] In our case the patient required treatment with IST in the first episode of HAA, and that allowed successful recovery of the bone marrow. In the second episode, however, the patient did not receive IST as he remained asymptomatic and his blood cell counts recovered spontaneously.

Recurrent HAA was reported once before by Muta T., *et al*. (2008).[12] In that case, the patient's first episode occurred at the age of 13, when he presented with acute hepatitis and severe pancytopenia. The etiology of the hepatitis was not identified and subsequently the patient was treated with cyclosporine for one year and maintained complete remission without treatment. Ten years later, he had a recurrent episode of HAA which required IST with antithymocyte globulin and cyclosporine.[12] Herein we report only the second case of recurrent HAA in the medical literature. In terms of etiology, we hypothesize that a second acute non-A-E viral infection, independent of the initial episode in childhood, may have resulted in a similar systemic immunologic response that adversely affected the bone marrow. It is also possible that a latent autoimmune disorder was re-activated by an environmental precipitant affecting both the liver and bone marrow.

CONCLUSION

Hepatitis associated aplastic anemia can be recurrent and occur many years after clinical remission of the first episode. Patients with HAA should be followed long-term and periodically screened as they remain at risk of recurrence.

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