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Case Report

Severe hepatitis-associated aplastic anemia following cytomegalovirus infection in an adult: a case report and literature review

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Abstract: Hepatitis-associated aplastic anemia (HAA), predominantly found in children, is a rare hematologic disease which follows the development of hepatitis. Cytomegalovirus (CMV) has been implicated as a cause of HAA. Here, a 25-year-old Chinese male, characterized by anemia, marked jaundice, scattered bleeding points on limbs, and left subconjunctival hemorrhage was described. Pancytopenia, reticulocytopenia, and hepatitis were identified in this case by laboratory tests, meeting the diagnostic criteria of HAA. Since CMV DNA was identified to be 9.69×10^8 copies/ml, this case was diagnosed as severe HAA following CMV infection (icteric type). By treatment of anti-human T lymphocyte porcine immunoglobulin (ALG, 2 g/d) combined with cyclosporine A (CsA, 300 mg/d), as well as magnesium isoglycyrrhizinate (MgIG, 150 mg/d) combined with phosphonoformic acid (PFA, 250 ml/12 h), pancytopenia, reticulocytopenia, and hepatitis were cured, and CMV DNA was reduced to 6.47×10^2 copies/ml. This case has been in stable condition until now. In clinical practice, attention should be paid on CMV infection in HAA cases. Aggressive immunosuppressive therapy (IST) combined with antiviral therapy may be an effective therapeutic strategy for severe HAA following CMV infection.

Keywords: Hepatitis, aplastic anemia, cytomegalovirus, immunosuppressive therapy

Introduction

Hepatitis-associated aplastic anemia (HAA) is a rare hematologic disease that occurs within several weeks or months after the occurrence of hepatitis, even during hepatitis convalescence [1]. HAA is predominantly found in children, adolescent boys, and young aged men [2]. If not treated in time, HAA is always fatal, exhibiting a high mortality of up to 85% [3]. Multiple non-A-E hepatitis viruses contribute to the occurrence and development of HAA, such as human parvovirus B19 (HPVB19), Epstein Barr virus (EBV), cytomegalovirus (CMV), transfusion transmitted virus (TTV), and echovirus [4]. CMV is a common viral agent contributing to a wide range of diseases in immunocompromised patients [5]. As a life-threatening complication of CMV infection, CMV induced HAA is rarely reported in adults. Here, a severe HAA following CMV infection was diagnosed in an adult male. This case was thoroughly cured by aggressive immunosuppressive therapy (IST) and antiviral therapy.

Statistical analyses

Statistical analysis was performed by SPSS version 17.0 (SPSS Inc., Chicago, IL). Comparison between different groups was determined by one-way ANOVA. A *p*-value less than 0.05 was considered to be significantly different.

Case report

A 25-year-old Chinese male was admitted to our hospital because of 6 days of hemorrhinia. He had no family history of hematopathy or liver diseases, and no record of recent infection. One month earlier, he had been admitted to a local community clinic because of anorexia and yellow urine, and diagnosed as hepatitis. Although liver protection and jaundice-relieving therapy were given, no improvement was

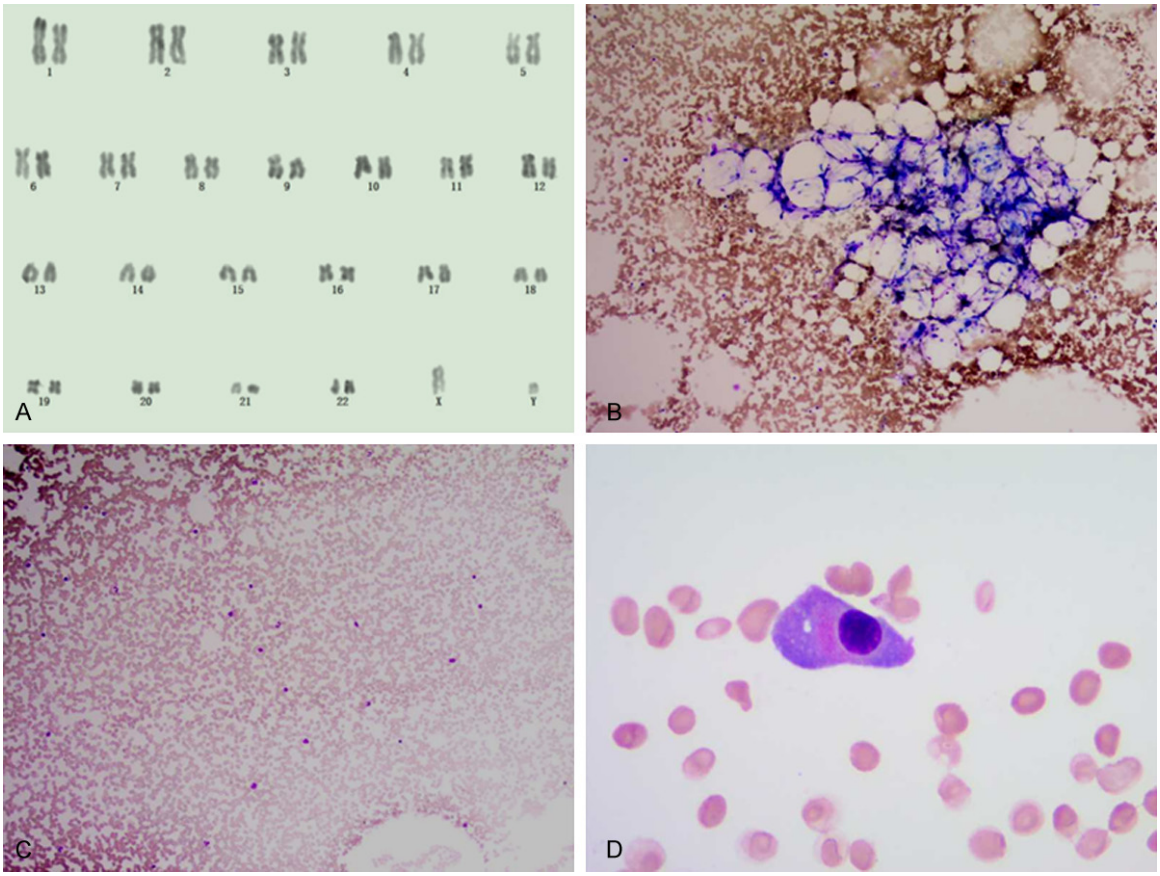

Figure 1. Bone marrow related indicators in diagnosis of aplastic anemia. (A) A normal karyotype (46, XY 20); (B) Partly empty bone marrow particles (Wright's staining, 100×), (C and D) Significantly reduced hematopoietic cells (Wright's staining, 100× C, 1000× D).

observed on this case. Five days prior to admission, pancytopenia was identified on this case by routine blood test (hemoglobin 97 g/L, leucocytes 3.0×10^9/L, neutrophils 2.5×10^9/L, and platelets 16×10^9/L).

On admission, this case exhibited symptoms of anemia, marked jaundice, scattered bleeding points on the limbs, and left subconjunctival hemorrhage. Pancytopenia and reticulocytopenia were diagnosed on this case by routine blood test (hemoglobin 79 g/L, reticulocytes 19×10^9/L, leucocytes 1.76×10^9/L, neutrophils 1.28×10^9/L and platelets 7×10^9/L). Hepatitis was diagnosed on this case by liver function test (alanine aminotransferase 1456 U/L, aspartate aminotransferase 436.2 U/L, total bilirubin 82.8 umol/L, direct bilirubin 59 umol/L, indirect bilirubin 23.5 umol/L, total protein 59.4 g/L, albumin 38 g/L and γ-glutamyl transpeptidase 110 U/L). Serological enzyme linked immunosorbent assay showed that this case was negative for hepatitis A, and E. Serological immunofluorescence assay showed that this case was negative for hepatitis B (HBsAg, 0.01 ng/ml; HBsAb, 70.01 mIU/ml; HBeAg, 0.096 NCU/ml; HBeAb, 0.15 NCU/ml; HBcAb, 0.01 NCU/ml), and C (HCVAb, 0.01 NCU/ml). Quantitative PCR showed that the CMV DNA was 9.69×10^8 copies/ml. Furthermore, this case was negative for tumor markers, antinuclear antibodies profile, and autoimmune liver disease-associated antibodies. Cytogenetic examination of aspirated bone marrow showed a normal karyotype (46, XY 20) (**Figure 1A**). Wright's staining of aspirated bone marrow showed that the bone marrow particles were partly empty, and the hematopoietic cells were significantly reduced (hypocellular marrow with trilineage myelodysplasia) (**Figure 1B-D**). The above manifestations met the diagnostic criteria of AA. This case was diagnosed as severe HAA following CMV infection (icteric type) at 7 days post-admission.

The therapeutic strategies for this case included administration of anti-human T lymphocyte porcine immunoglobulin (ALG, 2 g/d) combined

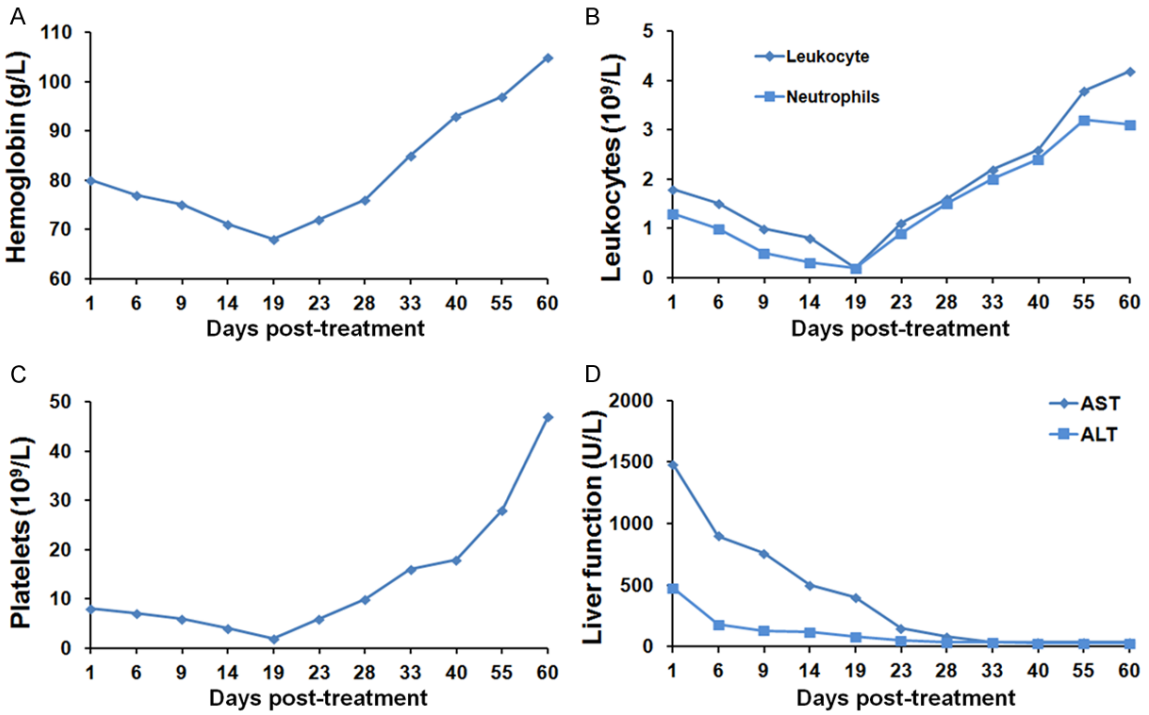

Figure 2. Routine blood and liver function of a patient with severe aplastic anemia following cytomegalovirus-associated hepatitis after the treatment of aggressive immunosuppressive therapy (IST) combined with antiviral therapy (1-60 days). A. Hemoglobin; B. Leukocytes and neutrophils; C. Platelets; D. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT).

with cyclosporine A (CsA, 300 mg/d), and magnesium isoglycyrrhizinate (MgIG, 150 mg/d) combined with phosphonoformic acid (PFA, 250 ml/12 h). Routine blood and liver function indexes were monitored every five days. Routine blood test showed that the levels of hemoglobin, leucocytes, neutrophils, and platelets progressively declined until the 19th day, and then gradually increased with aggressive treatments (**Figure 2A-C**). The aspartate aminotransferase (AST) and alanine aminotransferase (ALT) gradually decreased to normal levels with aggressive treatments (**Figure 2D**). One month later, the bleeding points on limbs and jaundice gradually vanished, and CMV DNA reduced to 6.47×10^2 copies/ml. Two months later, pancytopenia and reticulocytopenia disappeared (hemoglobin 106 g/L, leucocytes 4.2×10^9/L, neutrophils 3.1×10^9/L, platelets 47×10^9/L, and reticulocytes 19×10^9/L), and hepatitis was cured (ALT 34 U/L, AST 26.2 U/L, total bilirubin 28 umol/L, direct bilirubin 18.4 umol/L, indirect bilirubin 15.5 umol/L, total protein 67.6 g/L, albumin 46.8 g/L and γ-glutamyl transpeptidase 23 U/L). Then, this case was discharged.

After discharge, CsA and stanozolol were continued to be taken orally. Six months later, a normal blood routine was revealed (leucocytes 7.14×10^9/L, neutrophils 6.6×10^9/L, hemoglobin 136 g/L, platelets 119×10^9/L, and reticulocytes 48×10^9/L). CMV DNA was less than 5.0×10^2 copies/ml. This case is currently in stable condition.

Discussion

HAA is a rare hematologic syndrome following the development of hepatitis. Since first described by Lorenz and Quaiser in 1955, HAA cases have been reported by a larger number of researchers [4]. According to statistics between January 1998 and February 2013 from a previous study, the prevalence of HAA among AA cases was 3.8% (36/949), and the majority of HAA patients (33/36) were seronegative for a known hepatitis virus [6]. In this study, a 25-year-old Chinese male, characterized by pancytopenia, reticulocytopenia, and hepatitis was described. This case was diagnosed as severe HAA following CMV infection,

and thoroughly cured by IST and antiviral therapy.

Hepatitis viruses, such as hepatitis A, B, C, and E, are associated with HAA. However, serological detection found that hepatitis A, B, C, and E were all negative in our case. Non-A-E hepatitis viruses have also been implicated as a cause of HAA, such as HPVB19, EBV, CMV, and TTV, and echovirus [4]. For example, severe HAA combined with HPVB19 infection was revealed in a young male, exhibiting marked liver injury, prolonged jaundice, peripheral pancytopenia, and severe hypoplasia and fatty replacement [3]. A 73-year-old woman, characterized by intermittent fever, general weakness, elevated liver enzymes, and pancytopenia, was positive to EBV, and diagnosed as severe EBV infection with HAA [7]. A 17-year-old man with pancytopenia and severe acute hepatitis was positive to TTV [8]. In our case, a high level of CMV DNA (9.69×10^8 copies/ml) was revealed, which indicated that CMV infection contributed to the occurrence of HAA. CMV is a double-stranded DNA virus belonging to herpesviridae family. Due to the viral cytotoxic effects on specific tissues, CMV infection can lead to severe clinical manifestations in immunocompromised patients, especially in patients with history of transplantation [9]. It has been reported that, fatal CMV infection induced hepatitis secondary to IST treatment (r-ATG combined with CsA) was observed in a 21-year-old man with AA [10]. Severe colitis associated with both EBV and CMV secondary to ATG/CSP therapy was revealed in a 56-year-old man with AA [11]. A 44-year-old man characterized by 30 days of fever and progressive asthenia was diagnosed as CMV infection-induced hemolytic anemia [12]. Since CMV infection is not a routine test, the manifestation of CMV related complications may be underestimated. Therefore, CMV infection should be paid attention to in cases with HAA in clinical practice.

The pathogenesis of CMV induced HAA is complex. The following reasons have been considered: 1) CMV may inhibit the differentiation and proliferation of hematopoietic stem cells, or even induce chromosomal aberrations; 2) CMV may damage hematopoietic microenvironment in bone marrow; 3) since bone marrow cells exhibit a similar antigenicity with liver cells, bone marrow cells are also the attack target of CMV under the condition of CMV-mediated autoimmune abnormality; 4) CMV inhibits the detoxification function of liver, leading to the enhanced sensitivity of bone marrow cells to toxic drugs, thereby inhibiting hematopoietic function.

Currently, bone marrow transplantation (BMT) and IST are the main therapeutic strategies for severe HAA [13]. Allogeneic BMT is first-line therapy for HAA for its high cure rate (70%-90%) [14]. However, BMT cannot be undertaken promptly, because human leukocyte antigen-matched sibling donors cannot be easily found. IST is an alternative therapeutic strategy for HAA patient without the need of matched donors for BMT [15], exhibiting a 5-year survival rate of around 70% [3]. ATG and CsA, associate with response rates of about 50% are the most commonly used drugs in IST [16]. Both ATG and Cys can suppress cytotoxic T-lymphocytes, and improve hepatitis as well as bone marrow failure in HAA. The combined application of ATG and CsA is a good option for HAA in clinical practice, exhibiting a remission rate of 60-80% [16]. It has been reported that the complete remission rate and survival rate of HAA was 72% and 81%, respectively, after the first course of ATG and CsA treatment [17]. The outcomes of 44 HAA children who received 6 months of ATG and CsA showed that 14 (31.8%) cases achieved complete response and 17 (38.6%) achieved partial response, for an overall response rate of 70.4% [18]. In our case, 2 g/d ALG combined with 300 mg/d CsA was applied. After 1 month of treatment, favorable outcomes were observed on this case, including significantly increased hemoglobin, leucocytes, neutrophils, and platelets, and decreased AST and ALT. Two months later, pancytopenia and reticulocytopenia disappeared, and hepatitis was cured. Our findings were consistent with previous studies, and further illustrated that ATG combined with CsA is an effective therapeutic strategy for severe HAA. Since HAA was associated with CMV infection in our case, intravenous administration of 150 mg/d MgIG combined with 250 ml/12 h PFA was given. Quantitative detection showed that the CMV DNA was reduced to 6.47×10^2 copies/ml after one month of antiviral therapy. The remission of CMV infection may directly contribute to the recovery of HAA.

In conclusion, a 25-year-old Chinese male, exhibiting the symptoms of anemia, marked jaun-

dice, scattered bleeding points on limbs, and left subconjunctival hemorrhage was diagnosed with severe HAA following CMV infection. By the treatment of ALG combined with CsA, and MgIG combined with PFA, pancytopenia, reticulocytopenia, and hepatitis were cured on this case. CMV induced HAA, is characterized by an abrupt onset during the recovery period of hepatitis and exhibits no obvious prodrome or specific clinical manifestations. Since CMV induced HAA has a poor prognosis, it should be noticed in clinical practice, in order to achieve early diagnosis and treatment. At present, related studies on CMV induced HAA are still limited. Further research on diagnosis and treatment of CMV induced HAA based on more cases are urgently needed.

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Disclosure of conflict of interest

None.

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