CASE REPORT

Hepatitis-associated aplastic anaemia: a poor prognosis

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SUMMARY

A 13-year-old boy presented with spontaneous skin and mucosal bleeds 3 weeks after acute hepatitis of unknown aetiology. Laboratory analyses revealed pancytopenia and bone marrow biopsy that confirmed the diagnosis of aplastic anaemia. Other causes of congenital and acquired aplastic anaemia were excluded. He was diagnosed with hepatitis-associated aplastic anaemia. He developed a critical clinical condition, becoming totally dependent on erythrocyte and platelet transfusions, and severe neutropenia, which led to invasive bacterial infection. He died due to sepsis with multiple organ failure 3 months after admission.

BACKGROUND

Hepatitis-associated aplastic anaemia (HAAA) is a rare variant of acquired aplastic anaemia (AAA), in which an episode of hepatitis precedes the onset of aplastic anaemia. Bone marrow failure may be rapid and severe. It is usually fatal if untreated. It represents a life-threatening condition requiring prompt treatment. The aim of this case report is to highlight the high potential for morbidity and mortality of this disease.

CASE PRESENTATION

A previously healthy 13-year-old boy presented with spontaneous skin and mucosal bleeds for 1 week. There was no history of fever, weight loss, previous blood transfusion or exposure to drugs or toxins. His family history was uneventful. He had had choluria and jaundice 3 weeks earlier. Examinations conducted at the time were consistent with the diagnosis of acute hepatitis. Viral serologies showed no evidence of antibodies to hepatitis A, B or C. He was treated conventionally and recovered rapidly. On examination, he had moderate pallor of the skin and mucous membranes, generalised purpura and bruising. There were no signs of dysmorphism, jaundice or adenopathy.

INVESTIGATIONS

Laboratory tests revealed pancytopenia and reticulocytopenia with a normal peripheral smear (haemoglobin 9.1 g/dl, reticulocytes 20 000/mm³, leucocytes 1.4×10⁹/l, neutrophils 0.6×10⁹/l and platelets 2×10⁹/l) and hepatocellular injury (alanine aminotransferase 2222 U/l and aspartate aminotransferase 598 U/l).

Bone marrow aspiration and biopsy showed hypocellular marrow with depression of all three cell lines, thus meeting the diagnostic criteria of aplastic anaemia. There were no signs of fibrosis or

malignancy. A cytogenetic examination of the aspirated bone marrow showed a normal karyotype. Diepoxybutane-induced chromosomal breakage in peripheral blood was normal and excluded Fanconi's anaemia. The autoantibody screen and the thyroid function were normal. Direct/indirect Coomb's tests proved negative. The levels of B₁₂ and folates were within a normal range. Serological tests for hepatitis A, B, C, Epstein-Barr virus, cytomegalovirus, parvovirus B19, echovirus, enterovirus, herpes and HIV were negative. The chest x-ray showed no problems and the abdominal ultrasound indicated mild hepatomegaly.

OUTCOME AND FOLLOW-UP

The disease progressed with improvement of the liver function, but worsening of marrow failure. Severe pancytopenia with neutrophil count <0.2×10⁹/l persisted, meeting the criteria for very severe aplastic anaemia. He remained erythrocyte-dependent and platelet transfusion-dependent. No suitable human leucocyte antigen (HLA)-matched sibling donor (MSD) or unrelated donor for haemopoietic stem cell transplantation was found.

Within 5 days of admission, he developed persistent, continuous high-grade fever, despite treatment with broad-spectrum antibiotics and antifungal agents. Aetiological testing proved negative until 3 months later, when blood culture yielded *Staphylococcus hominis* and multiresistant *Klebsiella pneumoniae*. Directed antimicrobial therapy was started without leading to improvement. His clinical condition continued to deteriorate and he died due to pneumonia and sepsis with multiple organ failure 3 months after admission.

DISCUSSION

HAAA is a rare variant of AAA, in which marrow failure follows the development of hepatitis. It has been reported in 2–5% of cases in the West, and in 4–10% of cases in the Far East.¹

The presumed cause of hepatitis is still unknown. It may be induced by hepatitis B or C virus infection, and also by infections with other viruses, such as HIV, Epstein-Barr virus, transfusion-transmitted virus and echovirus.² However, most cases of HAA are seronegative for known hepatitis viruses, including hepatitis A, B, C and G.³ Clinical features and experimental results strongly suggest the presence of an immune-mediated pathogenesis. Two of the possible mechanisms of HAA, as well as of idiopathic aplasia, are T-cell mediated suppression of bone marrow, and liver infiltration by activated CD8 cells.⁴

To cite: Gonçalves V, Calado R, Palaré MJ, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2012-007968

Characteristically, the disease most often develops in adolescent boys and young men who develop severe pancytopenia 2–3 months after an episode of acute hepatitis.¹ Hepatitis shows variability in clinical features but generally follows a benign course, showing a partial or complete resolution before the onset of AA. A bone marrow failure can be rapid and severe, and is usually fatal if untreated. The mean survival rate after developing severe bone marrow aplasia has been 2 months, and the fatality rate ranges from 78 to 88%.^{5–7} In the case presented here, hepatitis had a favourable outcome, opposed to pancytopenia, which was very severe and developed earlier than described in the literature.

Likewise, severe AAA infection is an important cause of death. Profound persistent neutropenia is the dominant risk factor for the development of invasive bacterial and fungal infections.⁸ Regarding bacterial agents, coagulase-negative *Staphylococcus spp*, related to central venous catheters, predominates. Gram-negative infections are less common, due to the frequent use of antibiotics and the immunocompromised state of the AA patient.⁹ In our case, the emergence of a nosocomial multiresistant agent such as *K pneumoniae*, probably related to the prolonged use of antibiotics, potentially led to sepsis and multiple organ failure.

Since HAAA represents a life-threatening condition, its therapeutic approach should be considered as a medical emergency. First-line treatment is allogeneic haematopoietic stem cell transplantation from HLA-MSD. In patients without an available MSD, immunosuppressive therapy with cyclosporine and antithymocyte immunoglobulin is recommended. The survival of patients treated with haematopoietic cell transplantation and the response rate to immunosuppressive therapy were found to be 85% and 70%, respectively.¹⁰

In this case, besides not having a compatible donor for transplantation, the infection's severity and persistence within the initial days of admission delayed the initiation of immunosuppressive therapy, leading to an even worse prognosis.

Learning points

- Pancytopenia following hepatitis can be a potential life-threatening disease.
- Hepatitis-associated aplastic anaemia is a rare and severe variant of acquired aplastic anaemia.
- Prompt treatment is a requirement.
- The search for a matched related donor must be started immediately after diagnosis.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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