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REVIEW ARTICLE

Hepatitis-Associated Aplastic Anemia

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Abstract

Hepatitis-associated aplastic anemia (HAAA) is a rare illness, characterized by onset of pancytopenia with a hypoplastic bone marrow that traditionally occurs within 6 months of an increase in serum aminotransferases. HAAA is observed in 1% to 5% of all newly diagnosed cases of acquired aplastic anemia. Several hepatitis viruses have been linked to the disease, but in many cases no specific virus is detected. The exact pathophysiology is unknown; however, immune destruction of hematopoietic stem cells is believed to be the underlying mechanism. HAAA is a potentially lethal disease if left untreated. Management includes immunosuppression with antithymocyte globulin and cyclosporine and allogeneic hematopoietic stem cell transplantation.

Keywords: Aplastic anemia, Hepatitis

1. Introduction

Aplastic anemia (AA) is characterized by pancytopenia and hypoplastic "empty or fatty" bone marrow in the absence of bone marrow infiltrative disease. The disease was first described by Paul Ehrlich in 1888 [1]. Immune-mediated destruction of hematopoietic stem cells in the bone marrow is believed to be the underlying pathophysiology of the disease in the majority of cases [2]. This abnormal immune response may be elicited by exposures to various environmental agents such as toxins, chemicals, drugs, or viral infections. In a minority of causes, congenital bone marrow failure syndromes such as dyskeratosis congenita, Fanconi's anemia, or Shwachman–Diamond syndrome, can progress to frank AA. AA is associated with high mortality rates if left untreated.

Hepatitis-associated aplastic anemia (HAAA) is a rare but well-documented variant of AA in which marrow failure follows the development of hepatitis. HAAA has been defined as a variant of AA in which pancytopenia occurs concurrently or within 6 months of an increase of serum aminotransferase (ALT) more than five times the upper limit of normal [3-5]. The disease was first reported in two cases by Lorenz and Quaiser in 1955 [3]. Among 3,916 patients with AA reported to the European registry between 1990 and 2007, HAAA accounted for 1–5%[4]. The incidence is higher where hepatitis is prevalent, mostly in Asian countries [6,7], and in areas of low socioeconomic status [8,9].

Although in general AA does not appear to favor a particular race, age, or sex, HAAA has a slight male predominance and is more prevalent in adolescent males [4]. A 10-year retrospective study in Europe from 1997 to 2007 found that patients with HAAA are more likely to be younger (15 years vs. 20 years, $p < .001$) and male (68% vs. 58%, $p = .002$) compared with patients with AA not associated with hepatitis [4].

Several hepatitis viruses have been associated with HAAA, such as hepatitis A [10]; hepatitis B [4,11-13]; and hepatitis C [14], E, and G [15]. Viruses other than hepatitis viruses have also been

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implicated as a causative agents, such as parvovirus B19 [16-20], human herpesvirus 6 (HHV-6) [21], Epstein–Barr virus (EBV) [22], and non A–E hepatitis viruses (unknown viruses) [23].

2. Pathogenesis

In AA, cytotoxic T lymphocytes (CTLs) play an important role in the pathogenesis of AA and bone marrow destruction. The expansion of CTLs has been correlated with the severity of the disease. HAAA has been reported to arise even after liver transplantation in children with non-A, non-B, and non-C hepatitis-related liver failure, which suggests a continuum of the underlying pathogenesis even after the curative treatment of the inciting agent [24-26]. This observation, coupled with the response of HAAA to immunosuppressive agents, suggests a possible immunological pathogenesis for HAAA.

Various immunological abnormalities have been observed in patients with HAAA.

It has been postulated that common CTLs recognize similar target antigens between the liver and bone marrow cells in the early period of hepatitis. The expansion of these CTL clones leads to the subsequent destruction of bone marrow hematopoietic stem cells and AA [27,28]. There is also evidence that the ratio of CD4+/CD8 + in peripheral blood is lower in patients with HAAA compared to non-hepatitis associated AA, which could be helpful in predicting the development of HAAA [6,29,30]. Activated CD8 + lymphocytes have been shown to be cytotoxic to myelopoietic cells in the bone marrow in patients with AA [10]. The removal of lymphocytes from aplastic bone marrows improves colony numbers in tissue culture, and their addition to normal marrow inhibits hematopoiesis in vitro [31]. This may be mediated by interferon-gamma released by autoreactive T lymphocytes [32].

Regulatory T cells (Tregs) are believed to control and halt the progression of autoimmune disease by suppressing autoreactive T cells. It has been demonstrated that the number of Tregs in peripheral blood and bone marrow are reduced in acquired AA. This principle holds true in setting of HAAA as well [6].

There has been one report that looked into lymphocyte telomere length and found that patients with HAAA tend to have shorter telomere lengths compared to idiopathic AA. None of these patients had the clinical features of dyskeratosis congenita or its disease-causing mutation. This is important because dyskeratosis congenita can be associated with AA and hepatic abnormalities [33,34].

3. Clinical manifestation and diagnosis

Typically, AA starts to manifest during the recovery period from acute hepatitis [8]. The symptoms of hepatitis have been reported to range from mild hepatitis to fulminant hepatitis requiring liver transplantation.

Reports vary regarding the interval between the onset of hepatitis and the diagnosis of AA with a range between 3 months and 1 year [6,9,35,36]. There are no significant differences in the severity of AA between patients with HAAA and patients with idiopathic AA [37]. Patients with HAAA present with profound pancytopenia from weeks to months after an episode of acute, self-limited hepatitis. It is noteworthy to remember that hepatitis by itself can be associated with a transient decrease in blood counts, but the level of decrease in HAAA is more severe and potentially lethal if left untreated.

The clinical manifestations of pancytopenia include: spontaneous bleeding (mucosal or cutaneous) related to thrombocytopenia, an increased risk of infection secondary to neutropenia, fatigue, and pallor secondary to anemia. The most feared complication of HAAA is intracranial hemorrhage, which is very rare but potentially fatal.

Despite the association of several forms of viral hepatitis with HAAA, the serological and virological parameters for hepatitis A, B, and C were found to be negative in the majority of cases of HAAA [38]. This entity is sometimes labeled as "seronegative hepatitis aplasia."

A diagnosis of AA is suggested by the presence of pancytopenia (the simultaneous presence of anemia, thrombocytopenia, and neutropenia) with absolute reticulocytopenia. A bone marrow biopsy typically demonstrates profound hypocellularity affecting red blood cells and white blood cells precursors and megakaryocytopenia. These cells are typically replaced by fat cells and stroma without evidence of bone marrow infiltration or fibrosis.

The differential diagnosis of pancytopenia includes megaloblastic anemia, bone marrow infiltration (by various cancers or myelofibrosis), and myelodysplastic syndrome or acute leukemia. These disorders need to be excluded before diagnosis of AA is established.

4. Management and prognosis

HAAA is a potentially lethal disease if left untreated. Management of this condition involves supportive therapy and definitive therapies. Supportive therapies include blood and platelets transfusions using a restrictive transfusion approach to

avoid sensitization in patients who are candidates for hematopoietic stem cell transplantation (HSCT). All red blood cell units should be leukoreduced to minimize the risk of cytomegalovirus transmission and to lower the risk of febrile nonhemolytic transfusion reactions. Irradiation-depleted red blood cell units from lymphocytes and subsequently lowers the risk of transfusion-associated graft-versus-host disease. Patients with severe neutropenia are susceptible to life-threatening infections and should be treated with broad-spectrum antibiotics in setting of fever.

Similar to idiopathic AA, the definitive treatment options for HAAA are immunosuppressive therapy and allogeneic bone marrow transplant.

The response to immunosuppressive treatment in HAAA appears to be comparable to non-HAAA and reported to be around 70% [5,39]. In a study of 44 children with HAAA who received immunosuppressive therapy with antithymocyte globulin (ATG) and cyclosporine, 31.8% of the patients achieved a complete response and 38.6% achieved a partial response for an overall response of 70.4% after 6 months. The probability of survival at 10 years was 88.3 ± 4.9%. Although ATG and cyclosporine have the potential to cause hepatotoxicity, no hepatotoxicity of grades II–IV has been observed in this trial. This result supports the use of immunosuppressive therapy for patients who are not eligible for transplant [5].

ATG and cyclosporine are associated with a low risk for hepatitis B reactivation in patients with HAAA. In one report, the risk of hepatitis B reactivation in patients with hepatitis B surface antigen (HBsAg) was 4.76%. Patients with hepatitis B virus (HBV) reactivation had favorable clinical outcomes, with no HBV-related deaths [37]. This underscores the importance of closely monitoring HBV DNA, hepatic function and the possibility of antiviral prophylaxis in patients with AA and HBV infection who are getting immunosuppressive therapy.

Because of the rarity of HAAA, only a limited number of allogeneic bone marrow transplants have been performed. Allogeneic bone marrow transplant appears to be safe for use in HAAA. In a retrospective analysis of 37 Japanese adults who underwent allogeneic bone marrow transplantation, a third of whom had an alternative donor, the 5-year overall survival rate was 86% [7]. Using the same registry database, a recent report compared this result to patients with idiopathic AA and found out that they had a comparable survival (5-year survival, 85.7%) [7,40].

It is noteworthy that the presence of hepatitis at the time of transplant may alter the metabolism of some chemotherapy drugs used in conditioning regimen. In fact, one report suggests a dismal prognosis when myeloablative conditioning is used for allogeneic HSCT [41]. It has been established that fludarabine-based conditioning regimen is safe and effective and has a lower toxicity compared to cyclophosphamide-based conditioning regimen in patients undergoing allogeneic HSCT for AA [7,42,43]. Because HAAA is a rare disease and not all patients proceed to allogeneic HSCT, there are limited data regarding different conditioning regimens for this group. Despite this, fludarabine-based conditioning regimen appears to be safe and effective in this group of patients [7].

The risk for sinusoidal obstruction syndrome in HAAA appears to be small. For example, in the retrospective analysis of 37 adult Japanese individuals who underwent allogeneic HSCT, only one patient developed nonfatal sinusoidal obstruction syndrome [7].

HAAA is a severe disease that can be fatal if left untreated. Clinical trials are very limited in HAAA. The prognosis for HAAA is comparable to non-HAAA patients. Age and delayed treatment are the main negative indicators for survival according to a multivariate analysis [4].

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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