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Case Report

A Patient with Alcoholic Liver Cirrhosis Who Developed Autoimmune Hemolytic Anemia Following Infection with Influenza Type A

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Abstract

Influenza virus infection-induced autoimmune hemolytic anemia (AIHA) is extremely rare. This report describes a case of AIHA that was induced by type A influenza infection in a patient with alcoholic liver cirrhosis. In addition, a review of the medical literature regarding this subject is presented. A 67-year-old male with alcoholic liver cirrhosis was hospitalized with jaundice and ascites. At seven days after admission, type A influenza infection was diagnosed, which later progressed to hemolytic anemia. Direct and indirect Coombs tests were positive and anemia was diagnosed as warm-type AIHA. The anemia improved with prednisolone administration, but the patient died from hepatorenal syndrome at 14 weeks after admission.

ABBREVIATIONS

AIHA: Autoimmune Hemolytic Anemia; CAD: Cold Agglutinin Disease; PCH: Paroxysmal Cold Hemoglobinuria; LC: Liver Cirrhosis; Hb: Hemoglobin; T-bil: Total bilirubin; D-bil: Direct bilirubin; ITP: Idiopathic Thrombocytopenic Purpura; EBV: Epstein - Barr virus.

INTRODUCTION

Autoimmune hemolytic anemia (AIHA) is a general term for anemia caused by hemolysis due to an autoantibody attack on red blood cells [1-4]. Depending upon the optimum temperature for the autoantibodies, it is categorized as cold type [cold agglutinin disease (CAD) or paroxysmal cold hemoglobinuria (PCH)], mixed type, or warm type; the warm type is the most common [1,3,4]. AIHA can be idiopathic or secondary to drugs, solid carcinomas, and lymphoproliferative, autoimmune, and infectious diseases [1,3,4]. Although many viral infections can lead to AIHA [1,5-7], influenza infection or vaccine is rarely implicated in its occurrence: there are only 7 known cases in the English-language medical literature [8-13]. This article contains a case report of a patient with alcoholic liver cirrhosis (LC) who is thought to have developed AIHA from an influenza virus A infection and a review of the medical literature on this subject.

CASE PRESENTATION

The patient was a 67-year-old male with unremarkable medical history except a history of drinking approximately 900 mL (100 g of pure alcohol) per day for approximately 40 years. He had been undergoing treatment for alcoholic liver disease since 2003 at a local medical facility as an outpatient. His anemia did not worsen, and his hemoglobin (Hb) level was 11–12 g/dL. Around February 2007, he was admitted to a hospital in Kanagawa Prefecture for ascites and jaundice.

Physical findings were as follows: body temperature, 36.2°C; alert and lucid; no pallor in the palpebral conjunctiva, but a yellowish hue to the bulbar conjunctiva and skin. Cardiac and pulmonary sounds were normal, and the hepatosplenic region was not palpable. Ascites and swelling in the legs were observed. Results of tests performed at the time of hospitalization were as follows: WBC, 6,200/μL; Hb, 11.2 g/dL; platelet count, 9.4×10^4 /μL; hepaplastin test, 48%; total protein, 6.1 g/dL; albumin, 2.8 g/dL; total bilirubin (T-bil), 6.9 mg/dL; direct bilirubin (D-bil), 5.2 mg/dL; AST, 162 U/L; ALT, 43 U/L; Alp 1,079 U/L; and γ-GTP, 1,238 U/L. The patient was negative for HBs antigen; HCV antibody; and antinuclear, anti-smooth muscle, type 1 liver/kidney microsomal, anti-mitochondrial, and M2 antibodies. Abdominal CT and ultrasound revealed swelling in the hepatic left lobe as well as ascites and a swollen spleen, all of which are consistent with decompensated cirrhosis.

After hospitalization, intravenous administration of a diuretic and albumin alleviated ascites. On the 7th day of hospitalization,

the patient had a fever of 39°C, but signs and symptoms of pneumonia, urinary tract infection, spontaneous bacterial peritonitis, and other ascites-related infections were not observed, and the blood culture was negative. A rapid influenza diagnostic test via nasal swab was positive for influenza type A; therefore, oseltamivir (150 mg/day for 5 days beginning on the 7th day) was administered, and on the 11th day of hospitalization, the patient's fever was reduced. His Hb value decreased from 11 g/dL to 8.6 g/dL on the 16th day and to 7.4 g/dL on the 20th day. Test results on the 22th day were as follows: T-bil, 15.7 mg/dL (D-bil, 9.8 mg/dL) and LDH, 432 U/L. There was a ≥40% increase in reticulocyte count and a decrease in haptoglobin level (10 mg/dL). Test results were negative for cold agglutinin, but both direct and indirect Coombs tests were positive; the patient was diagnosed with warm AIHA. Platelet counts showed almost no change from before the onset of symptoms, and we suspected this was due to LC since complication (Evans syndrome) with idiopathic thrombocytopenic purpura (ITP) was not indicated. The patient was administered prednisolone (30 mg/day). At the start of this regimen, his Hb level was 4.6 g/dL, but 6 weeks later, it had improved to 6.9 g/dL. However, the liver failure progressed, and 14 weeks after hospitalization, he died of hepatorenal syndrome.

DISCUSSION

Events that result in AIHA include extravascular hemolysis caused by phagocytosis of erythrocyte-bound IgG in the spleen (hemolytic mechanism) and activation of polyclonal B cells, reactions to the molecular mimicry of exogenous antigens, breakdown of immunotolerance, and cytokine abnormality (autoimmune mechanism) [1-4]. The pathogenesis of AIHA secondary to viral infection may involve activation of B cells in response to the viral infection, production of autoantibodies in response to an exogenous antigen that is similar to autoantigens, activation of macrophages by cytokines expressed after viral infection, and acceleration of phagocytosis of erythrocyte-bound autoantibodies [5].

The reported types of secondary AIHA that occur after viral infection include warm AIHA caused by hepatitis A virus [7], Epstein-Barr virus (EBV), cytomegalovirus [6], and human parvovirus B19; CAD caused by EBV; and PCH caused by measles, rubella, and varicella viruses.

Hemolytic–uremic syndrome and ITP occurring after influenza virus infection have been previously reported [8]. Occurrence of AIHA after influenza infection is rare; there are only 2 reports in English-language medical literature [9,10]: Chen et al. [9] reported a 22-month-old boy who died of multiple organ failure several days after the administration of methylprednisolone for Coombs-positive Evans syndrome that occurred after influenza A virus infection. Schoindre et al. [10] reported a 60-year-old woman with diabetic nephropathy (end-stage renal disease) who died from CAD that occurred after influenza A virus infection.

There are five reports in English literature of AIHA occurring several days after influenza vaccination [8,11-13], thereby suggesting that the vaccines may be the cause: (1) a 9-year-old boy with Coombs-negative AIHA who went into spontaneous remission after only a blood transfusion (Tsuchiya et al. [11]); (2) a 50-year-old man with Coombs-positive Evans syndrome who went into remission after the administration of steroids and immunoglobulin (Shlamovitz et al. [8]); (3) a 59-year-old woman who developed Coombs-positive AIHA concurrent with a flare-up of systemic lupus erythematosus who went into remission after administration of steroids and azathioprine (Stratta et al. [12]); (4) an 83-year-old women with Coombs-positive AIHA who showed improvement after the administration of steroids and immunoglobulin (Montagnani et al. [13]); and (5) a 74-year-old woman with Coombs-positive AIHA who died 2 days after being hospitalized despite reduced anemia as a result of treatment (Montagnani et al. [13]).

Because the patient in our study received oseltamivir for the treatment of influenza infection, drug-induced AIHA must be considered. However, we have not found any reports of oseltamivir-induced AIHA in English-language medical literature [14-16], and in Japan, there was only one case in which oseltamivir was suspected to cause AIHA [17]. In this case (in contrast to what was observed in our patient), the patient's Hb levels were restored to normal approximately 2 weeks after oseltamivir treatment even though steroids were not administered. Furthermore, in the cases of drug-induced AIHA, ceasing the administration of the responsible drug almost always leads to rapid improvement [2]. In the present case, however, the persistence of anemia after cessation of drug administration suggests that the likely cause of AIHA was the influenza virus.

The drugs of choice for the treatment of warm AIHA are corticosteroids, because 70%–80% of patients respond to them [1,3,18,19]. Except in cases of CAD, steroids were used in all cases of warm AIHA caused by influenza virus infection [9] or vaccine [8,12,13]. Though the patient responded to steroids in this case, he died from hepatorenal syndrome. In the 2 reported cases of AIHA resulting from influenza infection, both patients died [9,10], whereas in the 5 cases of AIHA resulting from influenza vaccine, 1 died [13]. We believe the high mortality rate for the cases of AIHA related to the influenza virus is not due to a poor reaction to corticosteroid treatment, but due to serious complications.

In conclusion, this report describes a case in which a patient with alcoholic LC developed Coombs-positive AIHA caused by an influenza infection. Although this consequence is rarely observed, influenza virus infection-induced AIHA may be a fatal complication in cases with primary illnesses and in which the patient's general condition at the time of diagnosis is poor.

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