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Autoimmune Hemolytic Anemia Following Influenza Virus Infection or Administration of Influenza Vaccine

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Abstract

Autoimmune hemolytic anemia (AIHA) is caused by hemolysis induced by the reaction of autoantibodies with red blood cells. AIHA is categorized as warm, cold, and mixed types and as primary or secondary. Certain viral infections lead to secondary AIHA; however, AIHA induced by influenza virus infection or the administration of influenza vaccine is infrequent. Here, we review relevant case reports in the English and Japanese literature.

Keywords: Autoimmune hemolytic anemia; Influenza virus; Influenza vaccine

Introduction

Autoimmune hemolytic anemia (AIHA) is caused by hemolysis induced by the reaction of autoantibodies with red blood cells (RBCs) [1-4]. Events that lead to AIHA include extravascular hemolysis caused by phagocytosis of erythrocyte-bound IgG in the spleen (hemolytic mechanism), activation of polyclonal B cells, reactions induced by molecular mimicry of exogenous antigens, breakdown of immune tolerance, and abnormal cytokine expression (autoimmune mechanism) [1-4].

Evans syndrome is diagnosed by the simultaneous presence of AIHA, which is detected using a direct antiglobulin test (DAT), and immune (idiopathic) thrombocytopenic purpura (ITP) in the absence of an underlying etiology [5]. This syndrome is characterized by hemolytic anemia, thrombocytopenia, and the production of either antibodies, or complement, or both that attack RBCs and platelets [6].

Viral infections are associated with various hematological disorders caused by immune mechanisms, such as AIHA or Evans syndrome; however, influenza virus, which is highly prevalent, is an infrequent cause. For example, Sokol et al. [7] reported that only 8 (0.9%) of 865 patients with autoimmune hemolysis had "flu-like" illnesses. Furthermore, the administration of influenza vaccine infrequently causes immune hematological disorders such as AIHA [8].

To the best of our knowledge, there are no systematic reviews of AIHA cases that are induced by influenza virus infection or the administration of influenza vaccination. Therefore, we present here a review of relevant case reports in the English and Japanese literature since 1981.

Classification of AIHA

Based on the temperature optima of autoantibody reactivities, AIHA is categorized as cold [cold agglutinin disease (CAD) or paroxysmal cold hemoglobinuria (PCH)], mixed, or warm type [1,3,4]. The latter is most common and is frequently DAT (or Coombs test)-positive. Warm AIHA is estimated as partially DAT-negative, and Kamesaki et al. [9] indicated that patients with DAT-negative AIHA respond equally well to steroid therapy and have comparable 1-year survival rates when compared with patients with DAT-positive AIHA. AIHA is also classified as primary (idiopathic) or secondary. Secondary AIHA is induced by drugs, carcinomas, and by lymphoproliferative, autoimmune, and infectious diseases [1,3,4,10,11].

AIHA Associated with Viral Infections

Hepatitis A virus [12], hepatitis E virus [13], Epstein-Barr virus (EBV) [14], cytomegalovirus [15], and human parvovirus B19 [16] as well as others cause warm AIHA. EBV also causes CAD [17], and viruses causing diseases such as measles, rubella, and varicella also cause PCH [18].

The pathogenesis of AIHA secondary to viral infection may involve B cell activation in response to infection, autoantibody production in response to an exogenous antigen that mimics an autoantigen, macrophage activation by cytokines expressed after viral infection, and acceleration of phagocytosis of erythrocyte-bound autoantibodies [11].

Moreover, another possible mechanism of virus-associated AIHA is the reactivation of human herpesviruses, such as EBV or cytomegalovirus, although secondary AIHA by viral infection is usually due to primary infection. Dreyfus [19] reported that the reactivation of latent herpesvirus infection can directly alter host cytokine profiles and the expression of host transcription pathways. Moreover, Arai et al. [20] reported that EBV reactivation may worsen the severity of AIHA. Therefore, another possible mechanism of AIHA development may be the reactivation of latent herpesvirus infections induced by vaccine administration. However, to the best of our knowledge, there have been no case reports of AIHA induced by the reactivation of human herpesvirus after the administration of influenza vaccine. Thus, confirmation of AIHA induced by the reactivation of herpesvirus may provide new antiviral therapy options that are partially effective for autoimmune disorders, such as AIHA [21,22].

AIHA Associated with Influenza Infection

There are only three reports in the English medical literature (including cases of Evans syndrome) [6,23,24] and one in the Japanese

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literature [25] of AIHA after influenza virus infection. Teachey et al. [10] reported a child with B-cell precursor acute lymphoblastic leukemia who developed CAD during maintenance treatment while in remission after influenza type B infection. However, the authors were unable to determine whether the development of CAD was caused by the underlying lymphoid malignancy or influenza virus infection. Therefore, we excluded this case report from our list of AIHA cases that occurred after influenza virus infection.

The four AIHA cases following influenza virus infection are as follows: (1) Schoindre et al. [23] reported the case of a 60-year-old woman with diabetic nephropathy (end-stage renal disease) who developed CAD following influenza A virus (H1N1) infection. She died from severe respiratory failure and secondary bacterial infection that accompanied CAD 10 days after a diagnosis of influenza infection. (2) We reported a case of a 67-year-old man with alcoholic liver cirrhosis who died from hepatorenal syndrome approximately 12 weeks after the onset of influenza infection, although his Coombs-positive AIHA following influenza A virus infection responded to steroid treatment (Shizuma [24]). (3) Nagasaki et al. [25] reported the case of a 19-year-old female without a history of illness who was diagnosed with Coombs-negative AIHA following influenza virus A (H3N2) infection. Remission was induced using steroids. She was diagnosed with warm AIHA according to the high concentration of IgG that was bound to her erythrocytes. (4) Chen et al. [6] reported a 22-month-old boy who died of multiple organ failure several days after the administration of methylprednisolone to treat Evans syndrome that occurred after influenza A virus (H1N1) infection.

Because some patients received oseltamivir for the treatment of influenza infection, drug-induced AIHA must be considered during a diagnosis of influenza virus-induced AIHA. However, we did not find any reports of oseltamivir-induced AIHA in either the English or Japanese literature [26-28], and there was only one suspected case of AIHA that was caused by oseltamivir [29]. In this case, the patient's hemoglobin 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, terminating drug treatment almost always leads to rapid improvement [2].

AIHA Cases Followed by Administration of Influenza Vaccine

Although the mechanism of pathogenesis of autoimmune disorders induced by the administration of influenza vaccine is unknown, one possibility is the induction of an autoimmune response by molecular mimicry of host antigens by viral-derived peptides that induce cross-activation of autoreactive T or B cells [30]. The etiopathogenesis of autoimmune disorders induced by influenza vaccine remains unclear. However, mechanism-induce autoimmune responses may elicit cross-activation of autoreactive T or B cells [30].

There are five reports [5,30-32] in the English literature of AIHA that occurred several days after influenza vaccination (including cases of Evans syndrome), suggesting that the vaccinations may be the cause. The reports are as follows: (1) Tsuchiya et al. [31] reported the case of a 9-year-old boy who developed Coombs-negative AIHA five days after two influenza vaccinations. Remission was induced by administering a blood transfusion. (2) Stratta et al. [32] reported the case of a 59-year-old woman who developed Coombs-positive AIHA concurrent with a flare-up of systemic lupus erythematosus. She went into remission after the administration of steroids and azathioprine. (3) Montagnani et al. [30] reported the case of an 83-year-old woman who developed Coombs-positive AIHA approximately two days after the administration of influenza vaccine. Her anemia improved within two weeks after the administration of steroids and immunoglobulin. (4) Montagnani et al. [30] reported the case of a 74-year-old woman with aortic valvulopathy who developed Coombs-positive AIHA approximately three days after the administration of influenza vaccine. She died two days later after being hospitalized despite reduced anemia induced by treatment (corticosteroids and transfusion). (5) Shlamovitz et al. [5] reported the case of a 50-year-old man with no prior medical history who developed Coombs-positive Evans syndrome four days after the administration of influenza vaccine. Steroid and immunoglobulin treatment induced remission.

Conclusion

Influenza virus infection or the administration of influenza vaccine only infrequently induces AIHA. Patients with AIHA often achieve spontaneous or treatment-induced remission. However, AIHA associated with influenza infection or vaccination may be fatal in patients with primary illness who are in poor condition at the time of diagnosis.

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