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 [1,3,4,10]. 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 herpesviruses 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
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.

**References**


