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

Toru Shizuma*
Department of Physiology, School of Medicine, Tokai University, 143, Shimokasuya, Isehara, Kanagawa, 259-1193, Japan

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, Arau 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

*Corresponding author: Toru Shizuma, Department of Physiology, School of Medicine, Tokai University, 143, Shimokasuya, Isehara, Kanagawa, 259-1193, Japan. Tel: +81-0463-93-1121; Fax: +81-0463-93-6684; E-mail: shizuma@is.icc.u-tokai.ac.jp

Received February 12, 2014; Accepted February 21, 2014; Published February 26, 2014

Citation: Shizuma T (2014) Autoimmune Hemolytic Anemia Following Influenza Virus Infection or Administration of Influenza Vaccine. J Blood Disorders Transf 5: 200. doi: 10.4172/2155-9864.1000200

Copyright: © 2014 Shizuma T. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
et al. [30] reported the case of an 83-year-old woman who developed Coombs-positive AIHA concurrently with a flare-up of systemic lupus erythematosus. She went into remission 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**

1. Barros MM, Blajchman MA, Bordim JO (2010) Warm autoimmune hemolytic anemia: recent progress in understanding the immunobiology and the treatment. Transfus Med Rev 24: 195-210.
2. Gehrs BC1, Friedberg RC (2002) Autoimmune hemolytic anemia. Am J Hematol 69: 258-271.
3. Valent P1, Lechner K (2008) Diagnosis and treatment of autoimmune haemolytic anaemias in adults: a clinical review. Wien Klin Wochenschr 120: 136-151.
4. Michel M (2011) Classification and therapeutic approaches in autoimmune hemolytic anemia: an update. Expert Rev Hematol 4: 607-618.
5. Shlamovitz GZ1, Johar S (2013) A case of Evans’ syndrome following influenza vaccine. J Emerg Med 44: e149-151.
6. Chen H1, Jia XL, Gao HM, Qian SY (2011) Comorbid presentation of severe novel influenza A (H1N1) and Evans syndrome: a case report. Chin Med J (Engl) 124: 1743-1746.
7. Sokol RJ, Hewitt S, Stamps BK (1981) Autoimmune haemolysis: an 18-year study of 865 cases referred to a regional transfusion centre. Br Med J (Clin Res Ed) 282: 2023-2027.
8. Garbe E1, Andersohn F, Bronder E, Salama A, Klimpel A, et al. (2012) Drug-induced immune thrombocytopenia: results from the Berlin Case-Control Surveillance Study. Eur J Clin Pharmacol 68: 821-832.
9. Kamesaki T1, Toyotsui T, Kaji E (2013) Characterization of direct antiglobulin test-negative autoimmune hemolytic anemia: a study of 154 cases. Am J Hematol 88: 93-96.
10. Teachey DT, Felix CA (2007) Development of cold agglutinin autoimmune hemolytic anemia during treatment for pediatric acute lymphoblastic leukemia. J Pediatr Hematol Oncol 29: 397-399.
11. Musajai A1, Meite M, Detalle L, Franqui S, Cormont F, et al. (2005) Enhancement of autoantibody pathogenicity by viral infections in mouse models of anemia and thrombocytopenia. Autoimmun Rev 4: 247-252.
12. Kim HS, Jeong SH, Jang JH, Myung HJ, Kim JW, et al. (2011) Coinfection of hepatitis A virus genotype 7A and 7A complicated with autoimmune hemolytic anemia, prolonged cholestasis, and false-positive immunoglobulin M anti-hepatitis E virus: a case report. Korean J Hepatol 17: 323-327.
13. Thapa R, Ghosh A (2009) Childhood autoimmune hemolytic anemia following hepatitis E virus infection. J Paediatr Child Health 45: 71-72.
14. Sevilla J1, del Carmen Escudero M, Jiménez R, González-Vicent M, Manzanares J, et al. (2004) Severe systemic autoimmune disease associated with Epstein-Barr virus infection. J Pediatr Hematol Oncol 26: 831-833.
15. Veldhuis W1, Janssen M, Kortlandt W, van Houte A, van de Ree M (2004)
Coombs-negative severe haemolytic anaemia in an immunocompetent adult following cytomegalovirus infection. Eur J Clin Microbiol Infect Dis 23: 844-847.

16. Yagasaki H, Kato M, Shimizu N, Shichino H, Chin M, et al. (2011) Autoimmune hemolytic anemia and autoimmune neutropenia in a child with erythroblastopenia of childhood (TEC) caused by human herpesvirus-6 (HHV-6). Ann Hematol 90: 851-852.

17. Mason HM, Arndt PA (2008) A 13-year-old girl with cold agglutinin syndrome caused by anti-i. J Pediatr Hematol Oncol 30: 543-545.

18. Papalia MA, Schwarer AP (2000) Paroxysmal cold haemoglobinuria in an adult with chicken pox. Br J Haematol 109: 328-329.

19. Dreyfus DH (2013) Herpesviruses and the microbiome. J Allergy Clin Immunol 132: 1278-1286.

20. Arai A, Imadome K, Fujiwara S, Miura O (2010) Autoimmune hemolytic anemia accompanied by reactivation of an Epstein-Barr virus infection with suppressed CTL response to EBV-infected cells in an elderly man. Intern Med 49: 325-329.

21. Dreyfus DH (2011) Autoimmune disease: A role for new anti-viral therapies? Autoimmun Rev 11: 86-97.

22. Gentile I, Bonadies G, Buonomo AR, Minei G, Borrelli F, et al. (2013) Resolution of autoimmune thrombocytopenia associated with raltegravir use in an HIV-positive patient. Platelets 24: 574-577.

23. Schoindre Y, Bollée G, Dumont MD, Lesave F, Servais A (2011) Cold agglutinin syndrome associated with a 2009 influenza A H1N1 infection. Am J Med 124: e1-2.

24. Shizuma T (2013) A patient with alcoholic liver cirrhosis who developed autoimmune hemolytic anemia following infection with influenza type A. JSM Biotechnol Bioeng 2: 1019.

25. Nagasaki A, Oshiro A, Kinjo S, Oyamada T, Kajii E, et al. (2006) A case of Coombs-negative autoimmune hemolytic anemia following influenza A infection. Internal Medicine (Naika) 98: 742-744.

26. Garratty G (2004) Review: drug-induced immune hemolytic anemia—the last decade. Immunohematology 20: 138-146.

27. Pierce A, Nester T; Education Committee of the Academy of Clinical Laboratory Physicians and Scientists (2011) Pathology consultation on drug-induced hemolytic anemia. Am J Clin Pathol 136: 7-12.

28. Garratty G (2010) Immune hemolytic anemia associated with drug therapy. Blood Rev 24: 143-150.

29. Yagi Y, Yagi Y, Sageshima H, Miyata Y (2004) A case of infant with hemolytic anemia after oral oseltamivir administration. Acta Paediatr Jpn 108: 649-651.

30. Montagnani S, Tuccori M, Lombardo G, Testi A, Mantarro S, et al. (2011) Autoimmune hemolytic anemia following MF59-adjuvanted influenza vaccine administration: a report of two cases. Ann Pharmacother 45: e8.

31. Tsuchiya H, Ishii T, Fujiwara H, Matsuda I (1986) A case of Coombs-negative autoimmune hemolytic anemia, possibly caused by influenza vaccination. Acta Paediatr Jpn 28: 78-81.

32. Straat P, Cremona R, Lazzarich E, Quaglia M, Fenoglio R, et al. (2008) Life-threatening systemic flare-up of systemic lupus erythematosus following influenza vaccination. Lupus 17: 67-68.