Case Report

Autoimmune Hemolytic Anemia in a Renal Transplant Patient Following Seasonal Influenza Vaccination

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Vaccines aim to prevent disease occurrence, its severity, and resultant complications. Our patient, a 58-year-old male, received seasonal influenza vaccination as part of routine health maintenance. Three days later, he presented with malaise, fever, and yellowish discoloration of eyes. His labs showed hyperbilirubinemia, anemia, elevated lactate dehydrogenase, and low haptoglobin, consistent with hemolytic anemia. Autoimmune hemolytic anemia has been associated with vaccine use and may result from phenomena of molecular mimicry and cross-reactivity with the possible role of vaccine adjuvants as well. An underlying structural defect of the red blood cell membrane may make them prone to hemolysis. The differential diagnosis and work-up of hemolytic anemia is extensive, as performed in our case. Management strategies for vaccine-induced hemolysis may involve supportive care, red blood cell transfusion, steroids, and intravenous immunoglobulin.

1. Introduction

Seasonal influenza vaccine aims to protect against infection by influenza virus and resultant complications. Vaccines have been associated with autoimmune phenomena including triggering of autoimmune hemolytic anemias. Hemolytic anemia can present as chronic anemia secondary to chronic low-grade hemolysis or as brisk hemolysis leading to frank anemia that requires prompt medical treatment. Herein, we present a unique case of acute on chronic hemolytic anemia after a routine influenza vaccine in a kidney transplant patient.

2. Case Presentation

A 58-year-old Caucasian male with a past medical history of end-stage renal disease secondary to hypertension, hyperlipidemia, and diabetes mellitus type 2, received a living related kidney transplant in 1994. He was in his routine state of health with stable allograft function and was seen in internal medicine clinic for health maintenance visit where he received a seasonal influenza vaccine (0.5 ml intramuscular in the deltoid in October 2018—Quadrivalent Inactivated Influenza Vaccine IV4). Three days later, he presented with malaise, chills, fever (up to 101.6°F), and yellowish discoloration of eyes. His labs showed hyperbilirubinemia, anemia, elevated lactate dehydrogenase, and low haptoglobin, consistent with hemolytic anemia. Autoimmune hemolytic anemia has been associated with vaccine use and may result from phenomena of molecular mimicry and cross-reactivity with the possible role of vaccine adjuvants as well. An underlying structural defect of the red blood cell membrane may make them prone to hemolysis. The differential diagnosis and work-up of hemolytic anemia is extensive, as performed in our case. Management strategies for vaccine-induced hemolysis may involve supportive care, red blood cell transfusion, steroids, and intravenous immunoglobulin.
also been proposed [1]. Possible role of vaccine adjuvants has been proposed. Viral peptides inducing cross-reactivity by T-cells and B-cells.
available at reference laboratories. Patients with DAT/Coombs-negative AIHA may suffer milder anemia and hemolysis as compared to patients with DAT/Coombs-positive AIHA [10].

A negative DAT/Coombs in the presence of hemolysis may suggest an intrinsic erythrocyte defect of hemoglobin synthesis, enzymes, or membrane disorders. It may also suggest a nonimmune-mediated extrinsic hemolysis, which would include microangiopathic hemolytic anemia among other entities. The distinctive morphologic appearance of the red blood cells on a peripheral smear may be supportive of a specific diagnosis.

Initial work-up of anemia may include an iron profile as iron deficiency is a common cause of anemia, particularly when microcytic. To complete the work-up of anemia, hyperbilirubinemia, and hemolysis, exclusion of hepatitis with acute viral hepatitis panel may be appropriate as hemolysis can be seen in this setting. In our patient, hepatitis was excluded. Polymerase chain reaction for Parvovirus, Epstein–Barr virus, and cytomegalovirus was negative ruling out the other more common viral causes. Next, intrinsic causes of hemolysis such as hemoglobinopathies/thalassemias can be investigated via HPLC or hemoglobin electrophoresis. In our patient, hemoglobinopathy/thalassemia was ruled out by a normal HPLC. Also, the absence of microcytosis made thalassemia diagnosis unlikely. This is particularly important as cases of alpha thalassemia with only 1 or 2 gene deletions will have a normal HPLC. A common enzyme deficiency was ruled out by normal G6PD and pyruvate kinase levels. However, it is important to note that G6PD levels in a G6PD-deficient patient may be normal during acute hemolysis, necessitating repeat testing once hemolysis has subsided. A peripheral blood smear review by a pathologist is critical to further help diagnosis and subclassify hemolysis. This test should be utilized early on as it is potentially a cost-saving technique where the pathologist can suggest a possible cause and direct further testing. In our patient, this revealed prominent elliptocytosis.

Hereditary elliptocytosis, also called as ovalocytosis, is an inherited disorder in which the red blood cells are oval or elliptical rather than biconcave. It is caused by mutations in various genes eventually affecting the integrity of red blood cell membrane proteins and cytoskeleton. This leads to diminished mechanical stability of the RBC membrane making them prone to hemolysis. Most cases of hereditary elliptocytosis are due to mutations in the alpha-spectrin, beta-spectrin, or EPB41 genes. Diagnosis is usually made by review of the peripheral blood smear. The majority of patients with elliptocytosis are diagnosed incidentally as the disease is largely asymptomatic, as seen in our patient [11, 12]. Decompensated hemolysis resulting in symptomatic anemia may occur during acute illness or other conditions that impact red cell survival. This can be more severe in patients with underlying chronic hemolysis. In our patient, the influenza vaccine was the most likely culprit.

Piecing this together, the patient had an underlying hereditary elliptocytosis/ovalocytosis and was prone to chronic hemolysis due to diminished mechanical stability of the red blood cell membrane. Chronic low-degree persistent hyperbilirubinemia supported this diagnosis. In addition, the patient potentially developed an acute hemolytic insult from recent influenza vaccination.

Our patient was diagnosed with acute on chronic hemolytic anemia secondary to influenza vaccine with underlying hereditary elliptocytosis. A right upper quadrant ultrasound showed gallstones, which can be seen in patients with chronic hemolytic disorders (pigment stones), further supporting this diagnosis. In addition, the previously elevated bilirubin levels as well as prior noted elliptocytosis support this entity. The concordant acute AIHA diagnosis was supported by the development of hemolysis within a short time (3 days) after administration of influenza vaccine, absence of any new drug intake, and an extensive and negative work-up as mentioned above. The Naranjo algorithm used for determining the likelihood of adverse drug reaction due to the suspected drug categorized the event as “probable” adverse drug event. Of course, the elevated LDH, reticulocytosis, and suppressed haptoglobin support hemolysis in general.

5. Conclusion

Influenza vaccination may infrequently set off an episode of AIHA. The exact etiopathogenesis of such an event is not clearly understood. Molecular mimicry and role of vaccine adjuvants and other constituents have been proposed. An underlying erythrocyte membrane defect may act as a risk factor. Patients who receive an influenza vaccine should be counseled and educated about reporting any unusual signs and symptoms experienced after the vaccination.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

[1] S. Montagnani, M. Tuccori, G. Lombardo et al., “Autoimmune hemolytic anemia following MF59-adjuvanted influenza vaccine administration: a report of two cases,” *Annals of Pharmacotherapy*, vol. 45, p. 128, 2011.

[2] T. Shizuma, “Autoimmune hemolytic anemia following influenza virus infection or administration of influenza vaccine,” *Journal of Blood Disorders & Transfusion*, vol. 5, no. 3, 2014.

[3] G. Z. Shlamovitz and S. Johar, “A case of Evans’ syndrome following influenza vaccine,” *The Journal of Emergency Medicine*, vol. 44, no. 2, pp. e149–e151, 2013.

[4] H. Tsuchiya, T. Ishii, H. Fujiwara, and I. Matsuda, “A case of Coombs-negative autoimmune hemolytic anemia, possibly caused by influenza vaccination,” *Pediatrics International*, vol. 28, no. 1, pp. 78–81, 1986.

[5] L. Luzzatto, “Hemolytic anemias,” in *Harrison’s Principles of Internal Medicine*, 20e, J. Jameson, A. S. Fauci, D. L. Kasper et al., Eds., McGraw-Hill, New York, NY, USA, 2019, http://accessmedicine.mhmedical.com/content.aspx?bookid=21298&sectionid=192017418.

[6] T. Takahashi, “Direct antiglobulin test-negative autoimmune hemolytic anemia,” *Acta Haematologica*, vol. 140, no. 1, pp. 18-19, 2018.
[7] G. Garratty, “Immune hemolytic anemia associated with negative routine serology,” *Seminars in Hematology*, vol. 42, no. 3, pp. 156–164, 2005.

[8] G. B. Segel and M. A. Lichtman, “Direct antiglobulin ("Coombs") test-negative autoimmune hemolytic anemia: a review,” *Blood Cells, Molecules and Diseases*, vol. 52, no. 4, pp. 152–160, 2014.

[9] A. Salama, “Clinically and/or serologically misleading findings surrounding immune haemolytic anaemias,” *Transfusion Medicine and Hemotherapy*, vol. 42, no. 5, pp. 311–315, 2015.

[10] T. Kamesaki, T. Toyotsuji, and E. Kajii, “Characterization of direct antiglobulin test-negative autoimmune hemolytic anemia: a study of 154 cases,” *American Journal of Hematology*, vol. 88, no. 2, pp. 93–96, 2013.

[11] T. L. Coetzer, “Erythrocyte membrane disorders,” in *Williams Hematology, 9e*, K. Kaushansky, M. A. Lichtman, J. T. Prchal et al., Eds., McGraw-Hill, New York, NY, USA, 2019, http://accessmedicine.mhmedical.com/content.aspx?bookid=1581&sectionid=94304557.

[12] H. Bunn and S. E. Lux, “Inherited hemolytic disorders of the red cell membrane and red cell metabolism,” in *Pathophysiology of Blood Disorders, 2e*, J. C. Aster and H. Bunn, Eds., McGraw-Hill, New York, NY, USA, 2017.