

Severe Serum Sickness After H1N1 Influenza Vaccination

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Abstract: In this study, the case of a 48-year-old man with severe serum sickness reaction in response to H1N1 influenza immunization is reported. He presented with renal failure and several of the classic signs reported in early descriptions of serum sickness by Clemens von Pirquet and Bela Schick including lymphadenopathy, urticarial skin eruption and facial edema. Serum immunologic studies and tissue histology/immunohistochemistry assisted in firmly establishing the diagnosis in this case. With appropriate therapy, the patient's rash, edema and lymphadenopathy resolved and normal renal function returned. This first reported case of severe serum sickness to H1N1 vaccine is particularly important in light of the Centers for Disease Control and Prevention's recommendation for universal vaccination against influenza, including H1N1, in patients 6 months and older. With increasing numbers of patients receiving this vaccine, even rare adverse reactions may be experienced by numerous individuals. It is imperative that clinicians remain vigilant about possible reactions and quickly institute appropriate therapy.

Key Indexing Terms: Vaccination; Influenza; Serum sickness; Vaccine reaction. [Am J Med Sci 2013;345(5):412–413.]

Serum sickness was first characterized by Clemens von Pirquet and Bela Schick as a disorder resulting from antibody-antigen complexes created after exposure to foreign antigens.^{1,2} The original spectrum of symptoms included fever, lymphadenopathy, skin eruptions and edema and was later expanded to include arthralgias. Serum sickness is most commonly caused by drugs^{3–6} but has also been reported after vaccinations.^{7–11} Here, we describe the first reported case of severe serum sickness resulting from H1N1 influenza vaccine.

CASE REPORT

The patient is a 48-year-old man who presented to the emergency department (ER) with a chief complaint of facial swelling and shortness of breath. He was in his usual state of good health until 24 to 48 hours after receiving an H1N1 influenza vaccination. At that time, he developed facial swelling and rash predominantly on the anterior chest wall. This was followed by shortness of breath. Subsequently, he noted back pain, reduced urine output, brown urine and increasing swelling and rash, so was brought to the ER.

His medical history only included a cardiac surgery in Mexico at the age of 18, which per the patient was for a valvular problem. The patient had immigrated to the United States 11 years ago. He was on no medications and denied using over-the-counter medications, herbal supplements and illicit drugs before onset of the aforementioned symptoms. Before coming to the ER, he had taken diphenhydramine as treatment for the

rash. He denied upper respiratory tract and gastrointestinal symptoms in the 3-week period before presentation, and no lower respiratory tract symptoms were present before the aforementioned shortness of breath, which started after the onset of edema and rash. There was no history of recent insect sting or previous adverse reaction to stings. He reported having a tetanus vaccination in the past with no ill effect but had never had an influenza vaccination before. He denied any medication allergies.

In the ER, his blood pressure was 87/38 mm Hg, pulse 155 beats per minute and respiratory rate 30 breaths per minute. Respiratory distress with accessory muscle use was evident. Lungs were clear to auscultation. Face and neck displayed nonpitting edema, abdomen was distended and legs were edematous. Numerous wheals and raised erythematous plaques, some with central clearing consistent with urticaria, were present on the trunk and extremities. Mucosal surfaces were free of lesions.

White blood cell count was $22.2 \times 10^9/L$ including 20% neutrophils, 58% bands, 5% metamyelocytes/myelocytes, 3% eosinophils and 4% atypical lymphocytes. Blood urea nitrogen and creatinine levels were 27 mg/dL (reference range, 7–23 mg/dL) and 2.39 mg/dL (0.7–1.7 mg/dL), respectively, and increased to 86 mg/dL and 5.2 mg/dL. Fibrin degradation product level was $>20 \mu g/mL$ ($<5 \mu g/mL$). Erythrocyte sedimentation rate was 75 mm/hr. C3 and C4 levels were 29 mg/dL (86–184 mg/dL) and 8.9 mg/dL (20–59 mg/dL), respectively. Urinalysis revealed proteinuria.

Computed tomography scan revealed splenomegaly and extensive lymphadenopathy throughout the chest and abdomen. Infectious causes of the patient's symptoms were suspected, and a careful workup to exclude causative agents was undertaken. All cultures including aerobic, anaerobic, fungal and urine were negative. *Histoplasma* antigen was negative as was stool examination for ova and parasites. Assays for acute infection with *Coccidioides*, *Borrelia*, Epstein-Barr virus, cytomegalovirus, *Bartonella henselae*, *Brucella* and *Toxoplasma* were negative. Hepatitis panel, human immunodeficiency virus and assay for *Neisseria* DNA were also negative. Antistreptolysin titers were not suggestive of recent streptococcal infection. Immunoelectrophoresis revealed marked polyclonal increase in IgG and IgA. Bone marrow biopsy revealed polyclonal plasmacytosis only. C1q binding assay was 10.6 $\mu g/mL$ (0–3.9 $\mu g/mL$) indicating presence of circulating immune complexes. Skin biopsy revealed perivascular lymphocytic inflammation and marked dermal hemorrhage consistent with capillaritis (Figure 1), and immunofluorescence revealed focal vascular deposits of IgM and C3 in the dermis.

Prednisone 1 mg/kg/d was started. There was dramatic improvement in the rash in several days, and serum creatinine level decreased to 1.9 mg/dL. At 6-week follow-up, symptoms had completely resolved and renal function normalized. Because the patient and his wife denied any history of medication use, administration of antisera, blood products received, insect sting or recent illnesses in the 4- to 21-day period preceding onset of symptoms of serum sickness and no current infection was identified, the inciting factor was considered to be the influenza

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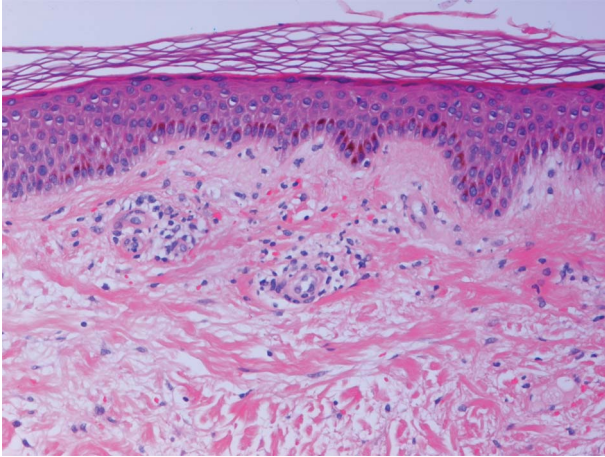


FIGURE 1. Several small vessels in the upper dermis with a mild lymphocytic infiltrate and many extravasated red blood cells.

vaccination. The clinic administering the vaccine reported this event via the Vaccine Adverse Event Reporting System.

DISCUSSION

Serum sickness is an uncommon adverse reaction caused by antibody-antigen complexes that deposit in the microvasculature.^{1,2} Complement is activated with consequential tissue damage.¹² With first-dose reactions, symptoms tend to develop 4 to 21 days after contact, as compared with onset as quickly as hours after subsequent encounters.²

Diagnosis is based on typical clinical manifestations and laboratory findings in the context of exposure to a foreign protein antigen. The presenting signs noted by von Pirquet were regional lymphadenopathy, fever, edema (especially facial) and a rash, typically urticarial.² Other symptoms are vomiting, arthralgias and rashes of other morphologies. Less commonly, neuropathy, arthritis and vasculitis may occur. Leukopenia, elevated erythrocyte sedimentation rate, and decreased C3 and C4 levels are frequently observed. Proteinuria, nephritis, thrombocytopenia and eosinophilia may also occur.³

Treatment begins with discontinuing the offending agent, and future avoidance is imperative. Supportive care may be sufficient in mild cases, and antihistamines and nonsteroidal anti-inflammatory drugs have been reported to be helpful.³ In severe cases, steroids are the treatment of choice, tapering over ≥ 2 weeks to avoid rebound.

Our patient developed symptoms 24 to 48 hours after H1N1 vaccination. Five to 6 weeks earlier, he had a febrile respiratory illness with malaise and aches, which was possibly a primary H1N1 infection. Reported local influenza infections were just past their peak at the time of that respiratory illness. Per Centers for Disease Control and Prevention surveillance reports, the occurrence was characterized as “regional,” and state surveillance reported cases of influenza in the county at that time. His wife reported that this was what prompted him to get an influenza vaccine though he had never had one in the past; he was trying not to become ill again. Unfortunately, he did not seek care at that time and was therefore not tested for influenza infection during that illness, so this remains a theory. If he indeed had developed circulating antibodies to influenza hemagglutinin or other proteins due to recent infection, this would explain his rapid reaction after vaccination. In this situation, the vaccination might be considered a second exposure,

and he would be expected to develop symptoms within 36 hours or less. Furthermore, his explosive onset and severity of symptoms are consistent with a second exposure event. No other potential cause of the event was discovered upon extensive history and laboratory evaluation. All clinical manifestations resolved with oral prednisone, and no relapse occurred. Rechallenge with vaccine was contraindicated and, therefore, not performed.

This case emphasizes the importance of early consideration of serum sickness in patients presenting with typical symptoms and recent exposure to a foreign antigen. Determination of causality in cases of suspected drug and vaccine adverse reactions could be challenging. Two recommended systems for evaluating causality are the World Health Organization-Uppsala Monitoring Centre causality assessment system¹³ and the algorithm developed by Halsey et al.¹⁴ In this case, the former, modified for vaccine use, was used to determine that the likelihood of the vaccine being the culprit agent was “probable.” Newly developed vaccines like the H1N1 influenza vaccination should be kept in mind as possible causes of serum sickness.

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