CASE REPORT

Serum sickness-like reaction after influenza vaccination

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SUMMARY

Serum sickness (SS) and SS-like reaction (SSLR) are rare immune complex-mediated hypersensitivity illnesses characterised by key features of fever, rash, polyarthralgia or polyarthritis. They are self-limiting with an excellent prognosis, settling as the antigen is cleared. We describe a 30-year-old man who presented with fever, rash, polyarthralgia and subcutaneous soft tissue swelling in his hands and feet at day 5 after influenza vaccination. A thorough investigation for infective and autoimmune causes for the presenting symptoms was negative. Given the temporal relationship between the symptoms and influenza vaccination, clinical evidence and biological plausibility of influenza vaccination causing SSLR, a clinical diagnosis of SSLR was made. The patient was treated with anti-histamines, non-steroidal anti-inflammatories and glucocorticoids with gradual resolution of symptoms over 5 weeks.

BACKGROUND

Serum sickness (SS) and SS-like reaction (SSLR) are rare in modern practice. This case depicts a rare adverse effect associated with vaccination. Influenza vaccination is important and is routinely recommended to the public prior to winter, when influenza incidence peaks. This report informs clinicians and readers about SSLR that may be caused by influenza vaccination. Therefore, it is important to elicit a thorough vaccination history in patients with suspected SSLR, as patients may not readily volunteer this information in their medical history.

CASE PRESENTATION

A 30-year-old man presented to hospital, with a 2-day history of generalised malaise, myalgia, chills and polyarthralgia of the shoulders, elbows, knees and hips. During the 24 h prior to hospital presentation, he developed an acute pruritic erythematous rash over his face, hands and feet. His hands and feet were also swollen. He had an influenza vaccination 5 days prior to his presentation and had received annual influenza vaccinations in the past without any adverse reaction. He denied any other infective symptoms.

There were no significant medical problems and he was not taking any medications. His family history was unremarkable. He had no known allergies.

He worked as a healthcare professional and was in a heterosexual monogamous relationship with his spouse. He was a non-smoker and rarely consumed alcohol.

On physical examination, he was febrile (38°C) and tachycardic (120 bpm). He was normotensive (125/80 mm Hg) and had a normal respiratory rate (18 breaths/min) with a normal oxygen saturation (100% on room air). He had an erythematous rash over his face (figure 1), hands (figure 2), ankles (figures 3 and 4) and the plantar surface of the right foot (figure 5). The rash was associated with significant subcutaneous tissue swelling and inflammation. He did not have any features of synovitis in any of his joints that would be suggestive of an inflammatory arthritis. His cardiovascular, respiratory, abdominal and neurological examinations were unremarkable.

INVESTIGATIONS

Investigations revealed a high C reactive protein of 149 mg/L (<5.0 mg/L), an elevated erythrocyte sedimentation rate of 53 mm/h (1–10 mm/h) and a moderately elevated white cell count of $12.2 \times 10^9/L$ ($4.0\text{--}11.0 \times 10^9/L$). Urine testing revealed mild haematuria without any infective features. Further testing of the urine with phase contrast microscopy revealed five dysmorphic red blood cells. He also had mildly elevated liver transaminases with alanine transaminases of 70 U/L (<55 U/L) and

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Figure 1 Multiple annular erythematous facial rash.

Figure 2 Subcutaneous tissue swelling and erythematous rash on the palmar surfaces of the right hand.

aspartate aminotransferase of 51 U/L (12–36 U/L). An ultrasound of the hands and feet revealed significant subcutaneous tissue swelling without tendonitis or synovitis. All other

Figure 3 Erythematous macular rash on the dorsal surface of the right ankle associated with subcutaneous tissue swelling.

Figure 4 Erythematous macular rash on the dorsal surface of the left ankle associated with subcutaneous tissue swelling.

investigations, including a bedside transthoracic echocardiogram, were unremarkable. Three sets of blood cultures from three different sites were collected. An autoimmune screen including complement levels and serology for hepatitis A, hepatitis B, hepatitis C, cytomegalovirus, Epstein-Barr virus, parvovirus, Barmah Forest virus and Ross-River virus were also collected.

Figure 5 Annular erythematous rash on the sole of the right foot.

DIFFERENTIAL DIAGNOSIS

- ▶ Viral exanthematous infections
- ▶ Hypersensitivity vasculitis and urticarial vasculitis
- ▶ Erythema multiforme
- ▶ Reactive arthritis
- ▶ Still's disease

TREATMENT

The patient was subsequently admitted under the infectious disease and immunology department. Given the patient was febrile, tachycardic and had elevated inflammatory markers, he was started on broad spectrum intravenous antibiotics, namely, flucloxacillin and gentamicin, to treat a possible infection with unclear focus. Later in the evening, the infectious disease physician made the diagnosis of SSLR secondary to influenza vaccination and ceased the antibiotics. The patient was discharged on symptomatic management with anti-histamines and anti-inflammatory medications.

OUTCOME AND FOLLOW-UP

A few days later, at outpatient follow-up, all the patient's blood cultures and serology were noted to be negative. His complement levels (C3, C4) were normal. Given the temporal relationship influenza vaccination, clinical evidence and biological plausibility of influenza vaccination causing SSLR, the clinical diagnosis of SSLR secondary to influenza vaccination was supported. Furthermore, there were no alternative diagnoses to explain the patient's symptoms.

The patient continued to develop rashes on his face, trunk, hands and feet over the next few weeks. These were initially managed with anti-histamines, which controlled the itch but did not control the rash. He was subsequently started on a weaning course of prednisolone starting at 25 mg daily and down-titrated by 2.5 mg every 3 days for 4 weeks. This strategy successfully controlled his rash outbreaks. He recovered fully after 5 weeks, which is consistent with the natural history of SSLR.

The patient decided not to receive influenza vaccination in future after weighing the risks and benefits. The efficacy of influenza vaccination is determined by the vaccination 'match' to the circulating influenza virus and the characteristics of the recipient of the vaccination. Therefore, the efficacy of influenza vaccination will vary each year and vary between individuals. Even though influenza vaccination is strongly recommended in healthcare workers, the SSLR that this patient experienced was debilitating and he was adamant that he would not receive further influenza vaccination, including other formulations such as nasal influenza vaccination or recombinant vaccinations. Besides, he may develop SSLR more rapidly and severely on re-exposure to the culprit antigen due to the pre-existing circulating antibodies (IgG) from previous exposure.

DISCUSSION

Vaccination is a safe and effective way to reduce the consequences of influenza infection in a community. At a community-based level, there is evidence for multiple benefits of influenza vaccination. However, individuals who receive the vaccine may have adverse events. A retrospective cohort study performed in Thailand revealed 14 of 495 healthcare personnel (3%) who received influenza vaccination developed SSLR postvaccination.¹ This case report further suggests that individuals may suffer adverse events to a vaccine that is generally effective. In terms of other case reports on influenza vaccine causing SS or SSLR,

there was one other case report of severe SS post H1N1 influenza vaccination.²

We described the events of fever, rash and polyarthralgia in a man following influenza vaccination, which we believed to be SSLR secondary to influenza vaccination. With individual adverse events following immunisation (AEFI), it is usually difficult to definitively determine the influenza vaccine as the culprit to explain the patient's symptoms. The SSLR in this patient could be a coincidental event. As influenza vaccination is given routinely on a large scale, it is inevitable that, after vaccination, recipients may suffer a significant health event. The health event is likely to be blamed on the vaccine based on the temporal relationship between the events. In this case causality was evaluated using the parameters of temporal relationship, biological plausibility, clinical evidence, laboratory evidence, population-based evidence and the possibility of alternative explanations attributing to the patient's symptoms.³⁻⁶ We are not able to state with certainty that influenza vaccination was the culprit for the patient's symptoms, but we could not find other explanations.

Influenza vaccine adverse reactions could be caused by vaccine antigens, vaccine adjuvants or vaccine constituents such as preservatives and stabilisers. The influenza vaccination that was given to this patient was Sanofi-Pasteur Vaxigrip. It is a sterile suspension of inactivated and purified influenza virus. Each 0.5 mL prefilled syringe (Vaxigrip) contains 15 µg haemagglutinin of each of the three strains in a buffered saline solution. The vaccine is prepared from virus grown in the allantoic cavity of embryonated eggs, inactivated by formaldehyde and then diluted in phosphate buffered saline solution to the required concentration. There are no adjuvants or preservatives added to this vaccine.⁷ A viral protein is the most likely antigen involved in this patient's SSLR.

Program errors leading to vaccine impurity can also be the cause of AEFI. This results from errors and accidents in vaccine manufacturing, handling and administration. They are preventable with good practice, and appropriate facilities and equipment.⁶ Given that there are no other similar reports in the healthcare institution that the patient is working at, it is unlikely that this event is associated to program error.

SSLR is a clinical diagnosis and there is no definitive investigation to confirm that this patient's symptoms were due to influenza vaccination. Laboratory testing is helpful to exclude other diagnoses. The principles of management of SSLR are withdrawal of the offending agent, symptomatic management and systemic glucocorticoids for more severe cases. SSLR has an excellent prognosis. Symptoms typically resolve within 2 weeks after withdrawal of the offending agent. However, in unusual cases, the symptoms of SS can last up to 2-3 months.⁸

Patient's perspective

- ▶ During the 5 weeks I was suffering from serum sickness, I had ongoing skin eruptions of migratory urticarial-type rashes. The glucocorticoids were successful in suppressing the rashes and the anti-histamines were very helpful in dealing with the itch caused by the skin rash.
- ▶ In the future, I will certainly be avoiding the influenza vaccination. It seems to me that it might be better catching the flu rather than having reactions like these!

Learning points

- ▶ Serum sickness-like reaction (SSLR) is a clinical diagnosis with key features of fever, rash and polyarthralgia/polyarthritis, and management is mainly symptomatic control and glucocorticoids.
- ▶ Influenza vaccination is commonly given to protect the community from influenza infection. SSLR can be caused by influenza vaccination.
- ▶ It can be difficult to determine with certainty the causality of individual adverse events following immunisation (AEFI). AEFI causality evaluation includes examining the clinical evidence, laboratory evidence, temporal association, biological plausibility, population-based evidence and possibility of alternative diagnosis. Outcomes of causality evaluation are classified into consistent causal association, indeterminate and inconsistent causal association.

Contributors FJKC was the patient affected in this case. He had his routine annual influenza vaccine prior to winter and, unfortunately, developed this rare reaction of serum sickness (SS) to the influenza vaccination. He thought it important to share his experience and so wrote this article. He also carried out a thorough literature review on SS. ML is the Director of Immunology and Infectious Disease Unit at the John Hunter Hospital, Newcastle, Australia. The patient was admitted under the care of ML, who also reviewed and edited this article. He also provided his expert opinion on this article. MB is an immunologist at John Hunter Hospital, Newcastle, Australia. He reviewed this article thoroughly and provided his expert opinion on SS and influenza vaccination. JA is a Consultant Physician and Professor of

Epidemiology and Public Health at the John Hunter Hospital, Newcastle, Australia. He reviewed and edited this article. He also provided his expert opinion on this article.

Competing interests None declared.

Patient consent Obtained.

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