Churg-Strauss Syndrome Following Vaccination Against 2010 Influenza A (H1N1): A Case Report

Mu-Hui Fu [1], Wan-Chen Tsai [1], Jui Lan [2], Cheng-Hsien Lu [1], Lian-Hui Lee [3], Chih-Cheng Huang [1]

Abstract-

Purpose and background: Churg-Strauss syndrome (CSS) is a systemic inflammatory disorder characterized by asthma, transient pulmonary infiltration, hyper-eosinophilia, and systemic vasculitis. Reported triggering factors include infections, drugs, allergic desensitization, and vaccinations, although cases involving the latter two are extremely rare. Herein, we describe a patient who developed CSS after receiving an H1N1 vaccination.

Case Report: A 55-year-old woman presented with fever, skin eruptions, and sensory impairment of her feet within one week after an H1N1 vaccine injection. A chest X-ray showed pulmonary infiltrations in both lower lung fields. Eosinophilia was noted in a hematological test, and an electrophysiological study revealed a pattern of mononeuritis multiplex. A skin biopsy was performed which revealed palisading necrotizing granuloma around a degenerated dermis and eosinophilic infiltration of the blood vessel walls. These findings combined with the hematological and electrophysiological findings met the criteria of CSS according to the American College of Rheumatology. The patient recovered well after steroid treatment.

Conclusion: This case highlights the possibility that the H1N1 vaccination can trigger CSS. Due to the rarity of reported autoimmune events after vaccine administration and the obscure causal association between autoimmunity and a vaccine, further post-marketing surveillance and research are necessary to clarify the relationship and identify risk factors.

Key Words: Churg-Strauss syndrome, H1N1, influenza vaccination, neuropathy, vasculitis

INTRODUCTION

Churg-Strauss syndrome (CSS) is a rare systemic necrotizing vasculitis of small and medium vessels that was first described in 1951 by the American pathologists J. Churg and L. Strauss in an autopsy series of patients with

severe asthma[1]. Clinically, the disorder is characterized by asthma, eosinophilia, transient pulmonary infiltration, and systemic vasculitis[2]. A diverse range of triggering factors have been reported, including infections, drugs, allergic desensitization and vaccinations[3], although cases involving the latter two are rare.

The influenza vaccine has been widely used worldwide for decades to control the pandemic spread of the influenza virus. Most of the known adverse effects following immunization such as transient injection site reactions (local erythema, soreness, and induration) or flu-like syndrome (myalgia, fever, and respiratory symptoms) are not life-threatening. Severe autoimmune reactions after influenza vaccination have rarely been reported.Herein, we report a patient who developed CSS after vaccination against influenza in 2010.

CASE REPORT

A 55-year-old woman who worked as a senior high school teacher was admitted to our hospital because of progressive painful numbness of her left foot for two weeks. She had been diagnosed as having left bundle branch block, mitral valve prolapse, and asthma nearly a decade previously. She denied the long-term use of any medication, although she intermittently used anti-histamines, steroids, and formoterol-plus-budesonide (Symbicort Turbuhaler) for asthma attacks.

She recalled receiving an H1N1 vaccine injection one month before admission. Two days after the vaccination, she had a fever of up to 38.9°C, with associated skin eruptions around the umbilicus and right nuchal area. A chest X-ray revealed pulmonary infiltrations in both lower lung fields. One week later, she noted a numbing sensation developing from her left sole extending to her left ankle and right sole. Due to an impaired postural balance, she also gradually experienced an unsteady gait.

A neurological examination on admission revealed anesthesia with impaired pinprick, light touch, vibration, and joint position sensations of her feet, and a positive Romberg's sign. There were no motor deficits or abnormal tendon reflexes. On physical examination, she had pruritic skin rashes on her neck and abdomen, but clear breathing sounds. Electrophysiological tests including nerve conduction study (NCS) and somatosensory evoked potential (SSEP) test were performed. The NCS showed absent responses in left tibial and left sural nerves, and a reduced amplitude in the right tibial nerve. An F response was absent in the left tibial nerve, whereas an H reflex was present and the latency was normal in bilateral tibial nerves (Table 1). In addition, SSEP showed normal results in both upper and lower limbs. A hematological test showed leukocytosis ($16,000/mm^3$) with increased eosinophils (63%, absolute eosinophil count 8966/μL) but no anemia (hemoglobin 13.9 g/dL). Rheumatological studies were negative for anti-nuclear antibody despite an elevated anti-rheumatoid factor (130 U/L; normal limit, <25 U/L) and positive for anti-neutrophil cytoplasmic antibody (ANCA). Routine urinalysis, renal, and liver function tests were all unremarkable. The pulmonary infiltration noted in the

Table 1. Results of nerve conduction study of the patient

Motor nerve conduction study			
Latency (ms)	Amplitude (mV)	MNCV (cm/s)	F wave latency (ms)
R Median			
Wrist 3.0	8.4	60.5	23.8
Ab Elb 6.8	7.8		
L Median			
Wrist 2.7	11.1	56.4	23.0
Ab Elb 6.6	10.3		
R Ulnar			
Wrist 1.9	7.1		25.3
Be Elb 5.1	6.5	56.6	
Ab Elb 6.9	6.3	55.6	
L Ulnar			
Wrist 2.2	6.2		25.0
Be Elb 5.0	5.5	64.3	
Ab Elb 6.9	5.4	52.6	
R Peroneal			
Ankle 3.3	4.2	47.9	46.0
Ab knee 10.4	4.0		
L Peroneal			
Ankle 3.4	3.6	47.2	44.5
Ab knee 10.6	3.9		
R Tibial			
Ankle 3.4	3.5	46.2	46.8
Knee 11.2	1.9		
L Tibial			
Ankle	No pick-up		N.R
Knee	No pick-up		

Table 1. Results of nerve conduction study of the patient

Sensory nerve conduction study			
	Latency (ms)	Amplitude (uV)	SNCV (cm/s)
R Median			
DigII - Palm	1.1	43.6	61.3
DigII - Wrist	2.0	39.7	65.0
L Median			
DigII - Palm	1.0	77.8	65.0
DigII - Wrist	2.2	64.4	59.1
R Ulnar			
Wrist - Dig5	1.7	24.7	63.6
L Ulnar			
Wrist - Dig5	1.8	51.9	62.1
R Sural			
Ankle - 14cm	2.6	8.7	53.8
L Sural			
Ankle - 14cm		No pick-up	
H reflex			
	Latency (ms)	Amplitude (mV)	
R Tibial			
M wave	6.7	0.06	
H wave	29.5	1.12	
L Tibial			
M wave	5.0	0.08	
H wave	28.8	2.28	

Abbreviations: MNCV, motor nerve conduction velocity; R, right; L, left; Ab, above; Elb, elbow; Be, below; SNCV, sensory nerve conduction velocity; DigII, the 2nd digital; Dig5, the 5th digital.

previous chest X-ray had disappeared in the repeat chest X-ray on admission.

On the night of admission, the patient had chest pain with elevated cardiac enzymes, and levels of troponin-I and CK-MB surged to 1.81 and 14.3 ng/mL, respectively. Non-ST-segment elevation myocardial infarction (NSTEMI) in the apical area was diagnosed based on electrocardiography findings and a thallium heart scan. Cardiac sonography also revealed small amounts of pericardial effusion. Her symptoms were relieved after the administration of enoxaparin.

Reviewing the patient's medical records, hyper-eosinophilia was noted prior to admission. Since she had no obvious source of allergy and no evidence of a parasitic infection, hyper-eosinophilic syndrome was diagnosed. Combining her clinical history, presentation, and examination findings (i.e., asthma, eosinophilia, pulmonary infiltration, and mononeuritis multiplex), she was suspected of having CSS based on the criteria of the American College of Rheumatology (ACR)[2].

A skin biopsy of the patient's upper back was performed for further confirmation. The results showed palisading necrotizing granuloma around a degenerated dermis and eosinophilic infiltration of the blood vessel walls, which were consistent with CSS (Fig. 1). She was therefore treated with 50 mg/day (1 mg/kg/day) of oral prednisone for one week, and the numbness of her feet improved greatly. In addition, the pericardial effusion was not found in follow-up cardiac sonography months later.

DISCUSSION

The pathophysiology of CSS is considered to be an autoimmune process because of the prominent allergic features, presence of immune complexes (48% are ANCA-positive), increased T-cell mediated immunity (Th2 predominance), and altered humoral immunity (elevated levels of immunoglobulin E and rheumatoid factor) [4]. Although the exact role of ANCA in CSS remains unclear, it is thought that the binding of ANCA to the vascular walls results in vascular inflammation leading to vasculitis. The histological findings of CSS include necrotizing vasculitis of small- and medium-sized vessels, eosinophilic infiltration, and granulomas. Although extravascular granulomas are characteristic of CSS, they can also be seen in other vasculitides, such as Wegener's granulomatosis[4]. Thus, histological features alone cannot be the basis for a definitive diagnosis, and the currently available criteria are mainly derived from clinical characteristics.

The most widely used diagnostic criteria at present are from the ACR[2], which include asthma, peripheral eosinophilia >10%, mono- or polyneuropathy, migratory pulmonary infiltration, sinus anomalies, and extravascular eosinophils in biopsy specimens. Four or more of the six criteria must be met for the diagnosis. The clinical manifestations of our patients met four of the criteria (i.e., asthma, peripheral eosinophilia >10%, pulmonary infiltration, and mononeuritis multiplex), and therefore
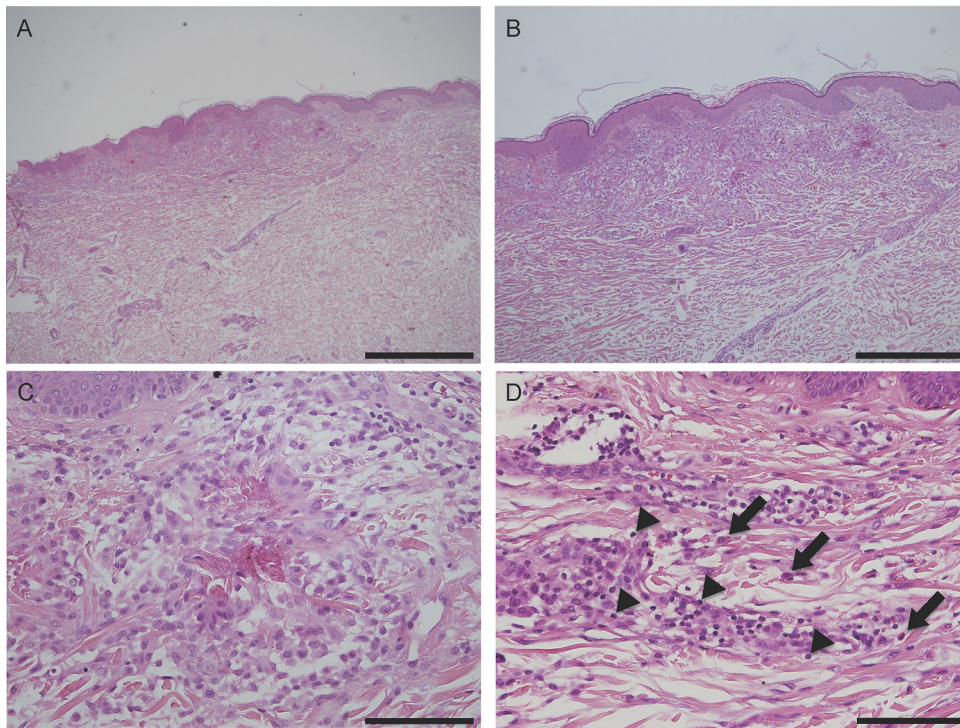
Figure 1. Skin biopsy sections from the patient's back, with hematoxylin and eosin (H&E) staining. (A) Moderately dense cellular infiltrates in the superficial dermis (magnification, 20X). (B) Lymphocytes and some eosinophils in the dermis and peri-vascular space (magnification, 40X). (C) Radially arranged histiocytes around degenerated collagen fibers form palisading necrotizing granuloma (magnification, 200X). (D) Peri-vascular lympho-histiocytic (triangular arrowheads) infiltration with some eosinophils (arrows) (H&E; original magnification, 200X).

CSS was diagnosed. In addition to the respiratory tract, other organ systems can also be affected in CSS patients. Vasculitis involving the gut, kidneys, and heart, as well as old age, have been suggested to be related to a poor prognosis[7]. Cardiac involvement is the most common cause of death for patients with CSS[8], and the apical NSTEMI and pericardial effusion seen in our patient were thought to be related to CSS.

The main neurological complication of CSS is peripheral neuropathy, which is one of the diagnostic criteria of CSS, although rare cases of cerebral infarction and cranial neuropathy have also been reported[5]. Necrotizing vasculitis mediated by cytotoxic T cells leading to ischemic changes appears to be the major cause of neuropathy associated with CSS, and mononeuritis multiplex is therefore the most common pattern[5,6]. The present case had neuropathies affecting bilateral tibial and left sural nerves (Table 1), and due to the asymmetric involvement polyneuropathy was less likely. In view of the simultaneous involvement of left tibial and sural nerves, left lumbosacral radiculopathy was possible. However, the intact tendon reflex in the lower limbs of this patient was surprising, and sparing of the peroneal nerve is atypical in such condition. A detailed review of the NCS results give us the answer. Although the patient had a lack of compound muscle action potentials (CMAP) and F wave response in the left tibial nerve and reduced CMAPs in the right tibial nerve, the H reflex in these two nerves was responsive with normal latency. The recording site for the H reflex was on the soleus muscle, and motor NCS and F wave studies of the tibial nerve were recorded on the abductor hallucis muscle. The dissociation between the results of H reflex and F wave (or motor NCS) suggests that the lesions of the tibial nerves were distal to the innervation to the soleus. As such, the patient had normal ankle jerks. The reason for the patient's normal

SSEP results is the same. The stimulation site of lower-limb SSEP was on the posterior tibial nerve just above the ankle, probably proximal to the lesion site. The normal SSEP results excluded the possibility of lesions in the proximal part of the tibial nerve, root, or spinal cord. Taken together, mononeuritis multiplex is much more likely to account for the manifestations seen in this patient. The distal lesion sites may also explain the patient's rapid recovery.

In terms of vaccine-associated autoimmunity, a problem has always existed in making a diagnosis due to the unclear criteria and few diagnostic tools. Stübgen suggested a framework proposed by Miller et al.[9,10]. In their opinion, an illness may be considered as being drug (or vaccine)-related when at least four of the following eight criteria are satisfied: 1) temporal association; 2) lack of likely alternative explanations; 3) stabilization/improvement of the disorder by interrupting exposure to the presumed inciting agent; 4) re-challenge; 5) biologic plausibility; 6) analogy; 7) dose responsiveness, and 8) specificity. In the present case, the criteria of temporal association, lack of likely alternative explanations, biologic plausibility, and analogy were met. The World Health Organization (WHO) causality assessment criteria and the Clinical Immunization Safety Assessment network modified criteria[11] are also widely used. These criteria focus primarily on the temporal relationship between vaccination and onset of adverse events, and other evidence supporting such an association is not required. The current patient's symptoms developed within one month after an influenza vaccine injection, and the clinical criteria of CSS were met at that time. Other differential diagnoses were excluded by the clinical, pathological, and laboratory findings. Overall, she met the WHO criteria as "very likely/certain" (clinical event with a plausible time relationship to vaccine administration that cannot be explained by concurrent disease or other drugs or chemicals).

Several autoimmune reactions after preventive anti-infectious vaccinations have been reported. Guillain-Barré syndrome has frequently been reported to be an autoimmune response following influenza vaccination[12,13]. Montagnani et al. reported two cases of autoimmune hemolytic anemia following an MF59-adjuvant influenza vaccination[14]. Other autoimmune responses related to influenza vaccination such as encephalitis, systemic lupus erythematosus, vasculitis, rheumatoid arthritis, and thrombocytopenia have also been reported[15,16]. To the best of our knowledge, there are only two reported cases of CSS induced by vaccination in the literature, both of which involved the hepatitis B vaccination[17,18].

The mechanism of vaccine-associated autoimmune diseases involves various factors such as molecular mimicry, epitope spread, polyclonal activation, and bystander activation [19]. Molecular mimicry is antigen-specific and often requires several days after the first exposure to an antigen because similarities in the amino acid sequence between the foreign antigen and self-peptides are sufficient to elicit cross activation of auto-reactive T or B cells by pathogen-derived peptides[20]. Epitope spread occurs as a result of an immune response against endogenous target antigens secondary to the release of self-antigens, which means that the immune reaction can attack different types of epitopes through a process of continuous damage. This phenomenon cannot happen without an initial episode of molecular mimicry[21]. Polyclonal activation, also termed polyclonal B cell response, is a process of one single antigen attacked by multiple clones of B cell through its overlapping epitopes. Bystander activation is a non-specific response mainly seen in studies of experimental animal models. It is based on the release of previously sequestered self-antigens or stimuli to the innate immune response in the infected host tissue, leading to the activation of antigen-presenting cells that present self-antigens and activate auto-reactive T cells[22]. Aside from antigenic-mediated responses, adjuvants can also induce autoimmune reactions. Adjuvants are agents used to non-specifically activate the innate immune system and enhance the adaptive immune response against the immunogen, thereby allowing the amount of antigen in the vaccine to be reduced. Adjuvants do not have specific antigenic effects by themselves and thus rarely induce autoimmune reactions. Although there is evidence showing that things can sometimes go wrong[19], it still remains difficult to confirm a clear causal relationship between adjuvants and post-vaccine autoimmunity. For the current patient, molecular mimicry and epitope spread may be the most likely inducing mechanisms. Polyclonal activation is the least likely because if there had been such a reaction, it would have

been noticed in the process of vaccine production or in clinical trials.

In summary, we present a case of CSS following an influenza vaccination. The impact of a vaccination on the immune system can hopefully be clarified through more case reports. Due to the rarity of reported autoimmune events after vaccine administration and the obscure causal association between autoimmunity and a vaccine, further post-marketing surveillance and research are necessary to clarify the relationship and identify risk factors.

REFERENCES

1. Churg J, Strauss L. Allergic granulomatosis, allergic angiitis, and periarteritis nodosa. Am J Pathol 1951;27: 277-301.
2. Masi AT, Hunder GG, Lie JT, Michel BA, Bloch DA, Arend WP, Calabrese LH, Edworthy SM, Fauci AS, Leavitt RY, et al. The American College of Rheumatology 1990 criteria for the classification of Churg-Strauss syndrome (allergic granulomatosis and angiitis). Arthritis Rheum 1990;33:1094-100.
3. Chusid MJ, Dale DC, West BC, Wolff SM. The hypereosinophilic syndrome: analysis of fourteen cases with review of the literature. Medicine 1975;54:1-27.
4. Finan MC, Winkelmann RK. The cutaneous extravascular necrotizing granuloma (Churg-Strauss granuloma) and systemic disease: a review of 27 cases. Medicine 1983;62:142-158.
5. Sehgal M, Swanson JW, DeRemee RA, Colby TV. Neurologic manifestations of Churg-Strauss syndrome. Mayo Clinic proceedings 1995;70:337-341.
6. Hattori N, Ichimura M, Nagamatsu M, Li M, Yamamoto K, Kumazawa K, Mitsuma T, Sobue G. Clinicopathological features of Churg-Strauss syndrome-associated neuropathy. Brain: a journal of neurology 1999;122:427-439.
7. Guillevin L, Pagnoux C, Seror R, Mahr A, Mouthon L, Le Toumelin P. The Five-Factor Score revisited: assessment of prognoses of systemic necrotizing vasculitides based on the French Vasculitis Study Group (FVSG) cohort. Medicine 2011;90:19-27.
8. Dennert RM, van Paassen P, Schalla S, Kuznetsova T, Alzand BS, Staessen JA, et al. Cardiac involvement in Churg-Strauss syndrome. Arthritis Rheum 2010;62: 627-634.
9. Miller FW, Hess EV, Clauw DJ, Hertzman PA, Pincus T, Silver RM, Mayes MD, Varga J, Medsger TA Jr, Love LA. Approaches for identifying and defining environmentally associated rheumatic disorders. Arthritis Rheum 2000;43:243-249.
10. Stubgen JP. Neuromuscular disorders associated with Hepatitis B vaccination. J Neurol Sci 2010;292:1-4.
11. Williams SE, Pahud BA, Vellozzi C, Donofrio PD, Dekker CL, Halsey N, et al. Causality assessment of serious neurologic adverse events following 2009 H1N1 vaccination. Vaccine 2011;29:8302-8308.
12. De Wals P, Deceuninck G, Toth E, Boulianne N, Brunet D, Boucher RM, Landry M, De Serres G. Risk of Guillain-Barre syndrome following H1N1 influenza vaccination in Quebec. JAMA 2012;308:175-181.
13. Greene SK, Rett M, Weintraub ES, Li L, Yin R, Amato AA, et al. Risk of confirmed Guillain-Barre syndrome following receipt of monovalent inactivated influenza A (H1N1) and seasonal influenza vaccines in the Vaccine Safety Datalink Project, 2009-2010. Am J Epidemiol 2012;175:1100-1109.
14. Montagnani S, Tuccori M, Lombardo G, Testi A, Mantarro S, Ruggiero E, Blandizzi C. Autoimmune hemolytic anemia following MF59-adjuvanted influenza vaccine administration: a report of two cases. Ann Pharmacother 2011;45:e8.
15. Morihara K, Arakawa Y, Takenaka H, Morihara T, Katoh N. Systemic lupus erythematosus following vaccination against 2009 influenza A (H1N1). Lupus 2011;20:775-756.
16. Schattner A. Consequence or coincidence? The occurrence, pathogenesis and significance of autoimmune manifestations after viral vaccines. Vaccine 2005;23:3876-3886.
17. Domiciano DS, Shinjo SK, Levy-Neto M. Churg-Strauss syndrome and active chronic hepatitis B virus infection: coincidence or association? Clinics (Sao Paulo) 2010;65:335-356.
18. Vanoli M, Gambini D, Scorza R. A case of Churg-Strauss vasculitis after hepatitis B vaccination. Ann Rheum Dis 1998;57:256-257.
19. Agmon-Levin N, Paz Z, Israeli E, Shoenfeld Y. Vaccines and autoimmunity. Nat Rev Rheumatol 2009;5:648-652.

20. Kohm AP, Fuller KG, Miller SD. Mimicking the way to autoimmunity: an evolving theory of sequence and structural homology. Trends Microbiol 2003;11:101-105.

21. Tchernev G, Orfanos CE. Antigen mimicry, epitope spreading and the pathogenesis of pemphigus. Tissue antigens 2006;68:280-286.

22. Salemi S, D'Amelio R. Could autoimmunity be induced by vaccination? Int Rev Immunol 2010;29: 247-269.