

Antivenin-related Serum Sickness

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Serum sickness is a type III hypersensitivity reaction that occurs due to the deposition of excessive circulating immune complexes in patients treated with foreign proteins or haptens. Serum sickness induced by antivenin for snakebites has been frequently reported in the USA, but not in Taiwan. This difference may be due to the efficacy and dosage of antivenins administered to treat snakebites in Taiwan. We report a case presenting with serum sickness after receiving a total of 20 vials of polyvalent antivenin therapy for the treatment of snakebite. A 59-year-old male suffered from fever, headaches, polyarthritis, and diffused skin rash approximately 10 days after administration of the antivenin. The large dose of antivenin administered in this case might have been the cause of the development of serum sickness. Physicians should be aware of the potential for serum sickness in cases of large-dose antivenin use. [*J Chin Med Assoc* 2010;73(10):540–542]

Key Words: antivenin, serum sickness, snakebite

Introduction

Serum sickness is an allergic disease that follows the administration of a foreign antigenic material, most commonly caused by injecting a protein or haptenic drug.¹ The disease is a type III hypersensitivity reaction mediated by deposits of circulating immune complexes in small vessels, which leads to complement activation and subsequent inflammation. Antivenin is 1 of the most frequent proteins known to elicit serum sickness.

Poisonous snakebites are an epidemiological problem worldwide, including in Taiwan.² The mainstay of treatment for venomous snakebites is antivenin,³ relying on an antidote to neutralize the venom to achieve detoxification. In the literature, the incidence of serum sickness induced by antivenin (Crotalidae) polyvalent (ACP) in the USA is reported to be as high as 40–80% in snakebite patients.^{3,4} In Taiwan, however, no cases of serum sickness related to antivenin have been reported, even with approximately 300–500 snakebite victims per year.² We report a Taiwanese patient who presented with serum sickness after receiving antivenin therapy for snakebite.

Case Report

A 59-year-old male was bitten by a *Trimeresurus stejnegeri* snake on the dorsum of the left hand while working in a field. One hour later, he presented to the China Medical University Hospital in Taichung, Taiwan. The dead snake was also available for species verification. On presentation, our patient's vital signs were stable, although he complained of pain in the bitten hand. Two fang marks were found with surrounding swelling and ecchymosis on the dorsum of the left hand. Laboratory data were unremarkable. In total, 20 vials of polyvalent antivenin (for *T. stejnegeri* and *Protobothrops mucrosquamatus*) were prescribed in the first 3 days due to progressive local swelling and persistent local painful sensation. Furthermore, fever was noted on the 2nd day after admission, and antibiotics (amoxicillin clavulanate) were prescribed for a total of 5 days for the treatment of cellulitis. No bacteria were identified in blood culture. The patient was discharged 7 days after admission with an improved condition.

However, intermittent fever and headaches developed 3–4 days after discharge. Pain, swelling, local heat, and limited joint movement in multiple joints of all



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4 limbs developed 2 days later. A diffuse skin rash with multiple erythematous itching papules and petechiae over both lower legs were also noted. Under the suspicion of serum sickness resulting from the antivenin treatment, the patient was readmitted for steroid treatment. Laboratory data showed an erythrocyte sedimentation rate of 30 mm/hour and a C-reactive protein level of 2.37 mg/dL (normal value, 0.8 mg/dL). C3 was 129 mg/dL (normal range, 79–152 mg/dL), C4 was 20.2 mg/dL (normal range, 16–38 mg/dL), and antinuclear antibodies and rheumatoid factor were negative. The episodes of arthritis and skin lesions improved after steroid treatment. The patient was discharged 5 days later.

Discussion

Serum sickness is the prototypic example of type III or immune-complex mediated hypersensitivity disease.¹ The reaction requires the presence of the antigen coincident with antibodies directed against the antigen, leading to the formation of an antigen-antibody or immune complex. These complexes are normally cleared by the mononuclear phagocyte system. Excess immune complexes may form in the circulation and deposit in tissues or form directly in the involved tissues if this system is not functioning well or is saturated by the immune complex load. The presence of immune complexes in parenchymal tissues, such as joints or lymph nodes, triggers an inflammatory response.

Our patient presented with the typical signs and symptoms of serum sickness such as rash, fever, malaise, and polyarthralgias or polyarthritis, which occur 1–2 weeks after the first exposure to the responsible agent. The laboratory results were also suggestive of inflammation. The patient's symptoms resolved within a few weeks of discontinuing the agent. Administration of antivenin treatment is the most plausible reason to explain the occurrence of serum sickness in this patient.

Products derived from horse serum and administered as antitoxins or antivenin are historically the most common cause of serum sickness. Previously, there was only 1 antivenin available in the USA (ACP) for the treatment of pit viper envenomation. The incidence of serum sickness induced by ACP can be as high as 40–80%.^{4,5} In a study by LoVecchio et al,⁴ patients of snakebite received an average of 38 vials of ACP (range, 5–62). The incidence of serum sickness can be expected to be greater than 50% in cases receiving 30–39 vials of antivenin and might reach 100% at doses of 40 or more vials. In recent years, a new antivenin (CroFab) composed of purified Fab segments specific to indigenous

snake species has been developed, and this has been shown to have a higher efficacy and fewer immunological effects.⁶ CroFab has a mean serum sickness incidence of less than 10%, with a range of 3–16%.⁷ The possible reasons for Fab antivenin-induced serum sickness are attributed to a high concentration of Fab fragments and contaminated Fc components.⁸

In Taiwan, however, reports of antivenin-induced serum sickness are rare, even with 300–500 snakebite victims per year.² This low frequency may be due to the efficacy and dosage of antivenins administered to treat snakebites in Taiwan. There are only 6 epidemiologically important poisonous snakes² and 4 kinds of lyophilized antivenin available to cover these 6 snakebites. These antivenins are produced by the Centers for Disease Control, Taiwan, in the form of F(ab)₂ fragments of an equine antigen. The antivenins contain 2,000 units per vial. A dose of 1–3 vials of antivenin should be adequate to treat mild-to-moderate snakebites, with the possible exception of a cobra snakebite.² These antivenins also have a low risk to induce acute adverse reactions.⁹ The patient in this report received a total of 20 vials of antivenin due to poor clinical response and eventually presented with symptoms consistent with serum sickness.

Serum sickness also results from the injection of other heterogeneous foreign proteins or haptens, and certain medications may cause serum sickness-like reactions. Cephalosporin antibiotics are 1 of the prototypes, with high rates of sickness-like reactions reported in children.¹⁰ A serum sickness-like reaction also occurs after penicillin administration and may be seen in some patients who receive prolonged, high-dose intravenous penicillin.^{11,12} During his first hospitalization after the snakebite, the patient in this case had been treated with amoxicillin clavulanate for possible cellulitis of the left hand. However, based on the time course, the episode of serum sickness developed 3–4 days after discharge and was most likely due to the antivenin. However, the role of antibiotics in the occurrence of serum sickness requires further investigation.

In conclusion, reports of serum sickness due to antivenins against snake venom are rare in Taiwan. However, physicians should remain alert to the potential for serum sickness in cases where large doses of antivenin are administered for snakebite.

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