



## Case Report

## Allergic reactions to antivenom in a patient bitten twice by the same snake within a month: A rare case report and literature review

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## ABSTRACT

Antivenom is the most effective method currently available for the treatment of poisonous snake bite. Allergic reactions to antivenom have been reported in the past. Here we shared a case of allergic reactions to antivenom in an old male patient who was bitten twice by the same snake (probably same one) at the same biting site within a month whereas the patient did not show any allergic disorder in the first bitten. Envenomations twice in a short period time by the same kind of snake are very rare. Physician should be alert to the occurrence of allergic reactions in treating this type of patients with antivenom. The skin allergy test has a certain value in predicting the allergic response before the second use of antivenom. Desensitization may reduce the incidence of allergic reactions, but this is insufficient. Rather than non-IgE-mediated immediate hypersensitivity, patients receiving the second treatment of antivenom may develop IgE-mediated immediate hypersensitivity. Once happened, the antivenom treatment should be stopped promptly and anti-allergy treatment should be given immediately.

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## Introduction

Anti-snake venom sera contain immune globulins or their fragments purified from plasma after the donor animals have been immunized with snake venom, and are mainly used for the treatment of envenomation.<sup>1</sup> The immunoglobulins in antivenom bind to the free toxins in the snake venom to neutralize the toxicity.<sup>2</sup> However, there are some adverse reactions in the use of antivenom, such as immediate hypersensitivity (8%) and serum sickness (13%).<sup>3</sup> It is a very rare condition that the patient was treated with the same antivenom. In this report, we present a case of envenomation treatment for an old male patient who did not have hypersensitivity in the first treatment, but developed immediate hypersensitive reaction during the second treatment with the same dose of serum after re-bitten by the same snake. We report the clinical manifestations, treatments, possible pathogenesis and preventative strategies.

## Case report

## Diagnosis and treatment

## First visit

The patient, male, 75 years old, had no previous history of drug allergy, asthma or allergic rhinitis. In the morning of September 26, 2015, the patient was bitten at the back of the right hand by a venomous snake in the kitchen (adder, a common snake in his area). The patients felt local pain and swelling that extended to the right forearm. No obvious wound bleeding, disturbance of consciousness, dizziness, nausea, vomiting, chest tightness nor dyspnea was found. He visited the hospital 1 h after the bite and received full examination.

The temperature was 36.5 °C, pulse 80 beats/min, respiratory rate 21 times/min, and blood pressure 116/88 mmHg. There was swelling from the back of the right hand to the right forearm. Two teeth marks were seeded at the wound site. Opisthenar was blue and purple in color with swelling; the fingers were inflexible. Blood routine tests showed that white blood cell count (WBC) was  $11.2 \times 10^9/L$ , the neutrophil ratio risen to 87% and others were normal.

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The patient was immediately given anti-adder venom (National Drug Approval No. S1082108, production lot number No. 20150501, Sailun Biological Technology, Shanghai, China) after skin allergy test showed negative result. The serum was intravenously infused with the dose of 6000 U and the patient showed no signs of allergy or other discomfort. The wound was debrided and topically applied with the powder of *Jidesheng* snake pill. Meanwhile, oral administration of the pill (8 g) and intramuscular injection of 15,000 U of refined tetanus antitoxin and 40 mg of methylprednisolone were done for anti-inflammation. Moreover intravenous drip of propacetamol (1 g) for pain relief and ceftazidime (2 g) for anti-infection was conducted. After one day of treatment, the swelling was subtotal subsided and opisthenar and fingers were flexible. The patient had no other discomfort and was discharged.

#### Second visit

On October 25, 2015, the patient was bitten again at the same site (the thumb and index finger of right hand) around 7:00. The snake was believed to be the same. The patient was severely painful with a small amount of bleeding in the wound. The patient had no dizziness, vertigo, numbness, heart palpitation, chest tightness, shortness of breath, nausea, vomiting, or abdominal pain. After treatment of the wound with ethanol by himself, the pain was not relieved. Thirty min later, the wound exacerbated with subcutaneous blisters appeared. The pain spread to opisthenar and extended to the upper limb. Opisthenar and the wrist were swollen, which did not subside after herbs application.

At 12 p.m., the patient visited the hospital. Physical examination showed that the temperature was 36.7 °C, pulse 82 beats/min, breathing 21 times/min and blood pressure 118/84 mmHg. The patient was conscious with smooth breathing and normal rhythm. The teeth marks of the snake were visible at the right thumb and index finger with local and dark-red swelling. There were some blisters and the swelling had extended to the upper arm from opisthenar. The circumferences 10 cm above the rasceta and olecranon were 23.5 cm and 30 cm, respectively. The same level of the sound limb was 21 cm and 26 cm, respectively. Opisthenar was heavily swollen with touch pain and normal skin temperature and slightly high tension. The five fingers were flexed with poor flexibility but normal feeling. Laboratory tests showed that WBC was  $15.6 \times 10^9/L$ , the neutrophil ratio 92.5%.

The patient was immediately given local debridement and rinsed with hydrogen peroxide, wound washing, oral administration of *Jidesheng* snake pill (8 g) and other anti-inflammation & anti-infection treatment as the first visit. Skin allergy test for antivenom was performed again but the result was positive with erythema papula of 2.2 cm in diameter. Upon obtaining the informed consent, the patient was desensitized and infused slowly (1 mL/min) with 6000 U serum in 500 mL saline according to the protocols approved by the CFDA (China Food and Drug Administration). The patient was transferred to the emergency room to receive desensitization treatment for 15 min along with ECG and oxygen saturation monitoring. He then felt hot at both feet but no other discomforts. 5 min later, he complained of dizziness, malaise, itching of chest and back, chills and cold extremities. Examinations showed that the respiratory rate was 22 times/min, pulse 98 beats/min, and blood pressure dropped to 98/49 mmHg. He had pale face with large area of erythema, rashes on the chest and swellings on the back. These symptoms were considered as allergic reactions and the infusion was stopped immediately. He was given oxygen, the oxygen concentration was 5 L per minute. He was also given intramuscular injection of Promethazine (1 mL) and intravenous injection of methylprednisolone (40 mg) and intravenous drip of 100 mL 10% glucose with 10 mL 10% calcium gluconate. Five min later, the patient achieved relief from the

symptoms and his complexion restored gradually with no more chills.

The temperature was measured to be 36.7 °C, breathing 21 times/min, heart beating 88 times/minute, blood pressure 121/88 mmHg and blood oxygen saturation 99%. One hour later, the rashes on the back and chest gradually faded and disappeared 6 hour later without other discomforts. He was later treated for swelling, pain, anti-infection as well as oral administration and topical application of snake pills. After 5 days of treatment, the pains and swelling were obviously relieved. Examinations showed that WBC was  $9.93 \times 10^9/L$ , neutrophil ratio of 69.5%. The patient was uneventfully discharged.

#### Case analysis

The same individual bitten by the same snake was reported very rarely. Our patient was bitten by the same kind snake (or very likely the same one snake as he said) within a month. The envenomations occurred at the same biting site. Clinical manifestations were similar and the second envenomation was accompanied with skin blisters and heavy swelling. The different clinical manifestations may be attributed to the dose, absorption and metabolism of the venom, as well as to the timing and dose of antivenom. According to the snake anatomy and detoxification methods, venom production cycle is generally 15–20 days. During biting, venom is injected into skin or muscle through the tooth and then diffused to the tissue space.<sup>4</sup> Most of the venom are the absorbed into the lymphatic system and 10 min after biting, venom antigens may be detected in blood, which peaked at 1.5–5 h.<sup>5</sup> Our patient visited the hospital respectively 1 and 5 h after the bite. Therefore, his clinical manifestations are likely dependent on the time.

It is not recommended by WHO to perform skin allergy test before the use of anti-venom serum.<sup>1</sup> Earlier study showed that there is not significant association between the results of skin allergy test and adverse reactions in the use of antivenom.<sup>6</sup> However, skin allergy testing is very useful in the diagnosis of many IgE-mediated immediate hypersensitivities to drugs, toxins and certain biological products.<sup>7</sup> According to the instructions for the antivenom, skin allergy tests are routinely performed. For this patient, the skin allergy test was positive at the second visit, however, antivenom treatment was still needed. The study showed that the use of epinephrine before antivenom can significantly reduce the incidence of adverse effects.<sup>8</sup>

Antivenom containing different immunoglobulin fragments have different incidence of allergic reactions [IgG (30%) > F(ab')<sub>2</sub> (10%) > Fab (0.8%)].<sup>9</sup> Richard once reported allergic reactions due to the use of antibody prepared with Fab fragment, which showed the symptoms of systemic urticaria, angioedema in oropharynx and tongue, drop of blood oxygen saturation to 88% and systolic blood pressure to 20 mmHg. All these symptoms are fully restored after giving anti-allergic, anti-histamine and epinephrine treatment.<sup>10</sup> However, these allergic reactions occurred when the patient received antivenom for the first time. Whereas our patient did not show any allergic reactions to antivenom at the first time but allergic at the second time with the same dose of serum. Therefore, the underlying mechanisms is likely different from what have been reported.

#### Discussion

A multicenter, randomized trial showed that the incidence of allergies to Fab antivenom is 19%.<sup>11</sup> Later on, there is a report on immediate allergic reactions following fast transfusion of antivenom.<sup>12</sup> However, subsequent study showed that the incidence of immediate allergic reactions is lower compared to the earlier reports, and the reactions are mild and easy to control.<sup>13</sup> So far, almost

all allergic reactions occur when the patients are infused with antivenom for the first time.

Anaphylaxis is a rapidly developing, life-threatening, systemic allergic reaction. Foods, drugs, and insect stings are the most common causes of this disorder. Classically, anaphylaxis is induced by antigen crosslinking of antigen-specific IgE that has bound to the high-affinity IgE receptor (FcεRI) on mast cells and basophils. This initiates signals induced cellular degranulation with release and secretion of vasoactive mediators, enzymes, and cytokines. Anyhow, acute allergic reactions mediated by IgE or non-IgE may result in similar early adverse events. Different mechanisms may have a primal role in anaphylaxis. IgE-dependent and distinct IgE-independent mechanisms can act together to increase anaphylaxis severity. Recognition of specific types of anaphylaxis is likely to become important for optimal prophylaxis and therapy.<sup>26</sup>

Non-IgE mediated allergic reactions account for most of the allergic reactions, which occur mostly in the patients who have never been exposed to antivenom.<sup>14</sup> Because of this, the skin allergy test is almost impossible to predict the occurrence of allergic reactions and therefore is not recommended.<sup>15</sup> Besides, IgG-mediated anaphylaxis should be suspected when there are large infusions of antigen and high titers of IgG antibody specific for the infused antigen, whereas complement-mediated anaphylaxis and direct mast cell/basophil activation should be suspected in patients who have received drugs, biologicals, or excipients that are known to have the appropriate complement or mast cell/basophil-activating properties.<sup>26</sup>

However for our patient, the allergic reactions occurred in the second time rather than the first time the patient was exposed to antivenom and therefore are likely IgE-mediated. To our knowledge, such IgE-mediated immediate hypersensitivity to antivenom has not been reported. This type of reaction mainly occurs in patients who has received animal-derived immune globulins and produced antibodies against the immune globulins. In our case, the patient had likely produced IgE antibody against antivenom. These IgE antibodies may react with FcεRI in the mast cells and basophils to quickly recognize antivenom proteins and induce cells to degranulate, then releasing vasoactive substances (such as histamine, interleukins and platelet activating substances), when the patient subsequently receives antivenom again. The release of these substances result in a number of clinical manifestations, such as vasodilation, increased vascular permeability and immediate hypersensitivity.<sup>16</sup> IgE is at very low level in normal human serum and highly variable. It's half time is only 2.5 days in the serum. However, once bound to receptors (such as FcεRI) on the surface of mast cells and basophils, it is stable for weeks to months.<sup>17,18</sup> In our patient, the time between the two treatments is about one month. The higher IgE content at the second treatment is most likely an indication of higher probability of allergic reactions.

But why didn't our patient have the anaphylaxis for the first time? Finkelman<sup>25</sup> thought that four results may occur, depending on antibody and antigen concentrations. Relative concentrations of antigen and antibody determine the roles of IgE and IgG antibodies in the setting of antibody-mediated anaphylaxis. IgE-mediated anaphylaxis requires considerably less antibody and antigen than IgG-mediated anaphylaxis. Consequently, when the antibody level is low, only IgE-mediated anaphylaxis will occur. When antigen levels are low but antibody levels are high, IgG "blocking" antibodies prevent IgE-mediated anaphylaxis by intercepting antigen before it can bind to FcεRI-associated IgE and by binding to the inhibitory receptor FcγRIIB, but the quantity of IgG/antigen complexes is too low to trigger IgG-mediated anaphylaxis. Therefore, anaphylaxis does not occur.<sup>25</sup> When antigen and antibody levels are both high but antibody levels are in excess to antigen levels, IgG antibodies block the binding of antigen to FcεRI-bound IgE, but IgG/

antigen complexes can bind to FcγRs; only IgG-mediated anaphylaxis occurs. When antigen and antibody levels are both high but antigen levels are in excess, IgG/antibody complexes are sufficient to trigger IgG-mediated anaphylaxis, and enough antigen escapes IgG blockade to bind to FcεRI-associated IgE and trigger IgE-mediated anaphylaxis. As for our patient, he was infused antivenom soon after snake bite at the first time. Antibody (antivenom) levels were high enough so that IgG intercepted antigen (snake venom) before it can bind to FcεRI-associated IgE, on the other hand, the quantity of IgG/antigen complexes is too low to trigger IgG-mediated anaphylaxis. That might be the reason why our patient did not show allergic reactions at the first biting treatment.

Though the 'bad side' of mast cells and IgE is so well accepted that it can be difficult to think of them in other contexts, particularly those in which they may have beneficial functions. There is evidence that mast cells and IgE, as well as basophils, can contribute to host defense as components of adaptive type 2 immune responses to helminthes, ticks and certain other parasites. IgE antibodies are produced against any of a diverse group of apparently harmless antigens, as well as against components of animal venoms.<sup>24</sup> Some unfortunate patients who are sensitized to venoms develop severe IgE associated allergic reactions, including fatal anaphylaxis, upon subsequent venom exposure. Stephen J. Galli and his league<sup>24</sup> found in mice which survive an initial encounter with venom, acquired type 2 immune responses, IgE antibodies, the high affinity IgE receptor (FcεRI), and mast cells can contribute to acquired resistance to the lethal effects of Russell's viper venom. This was unexpected because both IgE and IgG1 antibodies produced during type 2 immune responses can orchestrate anaphylaxis and other allergic reactions in mice and because type 2 immune responses against venoms (that include the development of antivenom IgG1 [in mice] and IgE antibodies) are classically thought to exacerbate the outcome of subsequent venom exposure. By contrast, IgG class antibodies raised against animal venoms, are used to treat envenomated humans or animals. But it is IgE antibodies that were the critical elements of the acquired host resistance to Russell's viper venom.<sup>23</sup> Consequently, it is not necessarily a bad thing for our patient generated IgE antibody after bitten by poisonous snakes.

The currently available antivenom contains three types of antibodies, which are IgG, F(ab')<sub>2</sub> and Fab fragments, and none of them is better than others.<sup>9</sup> Furthermore, due to variations of venoms in biochemical, pharmacological and immunological properties, it is still hard to make better choice of antibody. Commercially available antivenom is likely a mixture of antibodies that have different affinities to different venom. Even if the commercial monovalent antivenom in Australia is still polyvalent.<sup>19</sup> Anti snake venom serum of various types of antibodies, more or less residual Fc fragments, which for the human body is a heterologous substance, which caused the occurrence of allergic reactions is reasonable. Some studies showed that it may be feasible to reduce adverse reactions using antivenom prepared with highly immunogenic venom components that produce neutralizing and protective antibody after immunizing animals.<sup>20,21</sup> Needless to say, more efforts are needed to produce better antivenom for envenomation treatment. The research reported by Lei Zhang<sup>22</sup> suggested that they purified and immunoprotected of AaHIV from complex venom metalloproteinases of *deinagkistrodon acutus*. They demonstrated a basis for more efficient preparation of antivenom, which may provide a foundation for further screening and the preparation of antigen-specific epitope antigens by antigenomic technologies.

Envenomations twice in a short period time by the same kind of snake are very rare and care should be taken to the occurrence of allergic reactions in treating the type of patient with antivenom.

The skin allergy test has a certain value in predicting the allergic response before the second use of antivenom. Desensitization may reduce the incidence of allergic reactions, but is not sufficient. Patients receiving the second antivenom might have IgE-mediated immediate hypersensitivity. Once occurring, the antivenom treatment should be stopped immediately and anti-allergy treatment should be given immediately.

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## References

- Warrell DA. *Guidelines for the Management of Snake-bites*. WHO Regional Office for South-East Asia; 2010:77–79. <http://www.searo.who.int/entity/emergencies/documents/9789290223774/en/>.
- Gutierrez JM, Leon G, Burnouf T. Antivenoms for the treatment of snakebite envenomings: the road ahead. *Biologicals*. 2011;39:129–142.
- Schaeffer TH, Khatri V, Reifler LM, et al. Incidence of immediate hypersensitivity reaction and serum sickness following administration of Crotalidae polyvalent immune Fab antivenom: a meta-analysis. *Acad Emerg Med*. 2012;19:121–131.
- Ownby CL. Structure, function, and biophysical aspects of the myotoxins from snake venoms. *Toxin Rev*. 1998;172:213–238.
- Paniagua D, Vergara I, Boyer L, et al. Role of lymphatic system on snake venom absorption. In: Gopalakrishnakone P, Inagaki H, Mukherjee AK, eds. *Snake Venoms*. Berlin: Springer Netherlands; 2015:1–19.
- Malasit P, Warrell DA, Chanthavanich P, et al. Prediction, prevention, and mechanism of early (anaphylactic) antivenom reactions in victims of snake bites. *Br Med J Clin Res Ed*. 1986;292:17–20.
- Bernstein IL, Li JT, Bernstein DI, et al. Allergy diagnostic testing: an updated practice parameter. *Ann Allergy Asthma Immunol*. 2008;100:S1–S148.
- Williams DJ, Jensen SD, Nimorakiotakis B, et al. Antivenom use, premedication and early adverse reactions in the management of snake bites in rural Papua New Guinea. *Toxicon*. 2007;49:780–792.
- Theakston RD, Warrell DA, Griffiths E. Report of a WHO workshop on the standardization and control of antivenoms. *Toxicon*. 2003;41:541–557.
- Clark RF, McKinney PE, Chase PB, et al. Immediate and delayed allergic reactions to Crotalidae polyvalent immune Fab (ovine) antivenom. *Ann Emerg Med*. 2002;39:671–676.
- Dart RC, Seifert SA, Boyer LV, et al. A randomized multicenter trial of crotalinae polyvalent immune Fab (ovine) antivenom for the treatment of crotaline snakebite in the United States. *Arch Intern Med*. 2001;161:2030–2036.
- Holstege CP, Wu J, Baer AB. Immediate hypersensitivity reaction associated with the rapid infusion of Crotalidae polyvalent immune Fab (ovine). *Ann Emerg Med*. 2002;39:677–679.
- Cannon R, Ruha AM, Kashani J. Acute hypersensitivity reactions associated with administration of Crotalidae polyvalent immune Fab antivenom. *Ann Emerg Med*. 2008;51:407–411.
- da Silva IM, Tavares AM. Comparative evaluation of adverse effects in the use of powder trivalent antivenom and liquid antivenoms in Bothrops snake bites. *Rev Soc Bras Med Trop*. 2012;45:523–525.
- Meenatchisundaram S, Parameswari G, Michael A, et al. Neutralization of the pharmacological effects of Cobra and Krait venoms by chicken egg yolk antibodies. *Toxicon*. 2008;52:221–227.
- Leon G, Herrera M, Segura A, et al. Pathogenic mechanisms underlying adverse reactions induced by intravenous administration of snake antivenoms. *Toxicon*. 2013;76:63–76.
- Roitt I. *Immunology*. 6th ed. Harcourt Asia Pte Ltd.; 2001:324–325.
- Platts-Mills TA. The role of immunoglobulin E in allergy and asthma. *Am J Respir Crit Care Med*. 2001;164:S1–S5.
- Rusmili MR, Yee TT, Mustafa MR, et al. In-vitro neurotoxicity of two Malaysian krait species venoms: neutralization by monovalent and polyvalent antivenoms from Thailand. *Toxins (Basel)*. 2014;6:1036–1048.
- Gutierrez JM. Improving antivenom availability and accessibility: science, technology, and beyond. *Toxicon*. 2012;60:676–687.
- Frauches TS, Petretski JH, Arnholdt AC, et al. Bothropic antivenom based on monoclonal antibodies, is it possible? *Toxicon*. 2013;71:49–56.
- Zhang L, Chen C, Cao Y, et al. Purification and immunoprotection evaluation of AaHIV from complex venom metalloproteinases of *Deinagkistrodon acutus*. *J Biochem Mol Toxicol*. 2016;30:470–476. <http://dx.doi.org/10.1002/jbt.21813>.
- Starkl P, Marichal T, Gaudenzio N, et al. IgE antibodies, FcεRIα, and IgE-mediated local anaphylaxis can limit snake venom toxicity. *J Allergy Clin Immunol*. 2015;137:246–257.
- Galli SJ, Starkl P, Marichal T, et al. Mast cells and IgE in defense against venoms: possible “good side” of allergy? *Allergol Int*. 2015;65:3–15.
- Strait RT, Morris SC, Finkelman FD. IgG-blocking antibodies inhibit IgE-mediated anaphylaxis in vivo through both antigen interception and FcγRIIb cross-linking. *J Clin Invest*. 2006;116:833–841.
- Finkelman FD, Khodoun MV, Strait R. Human IgE-independent systemic anaphylaxis. *J Allergy Clin Immunol*. 2016;137:1674–1680.