Case Report

A rare manifestation of serum sickness after common krait envenomation in a patient treated with polyvalent anti-snake venom in India: Presentation and challenges

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Abstract

Envenomation from snakebites is a significant public health concern in the Southeast Asian region resulting in considerable mortality and morbidity. Anti-snake venom (ASV) despite being the only rescue can bring forth several acute and delayed adverse effects. Among them, serum sickness is a late manifestation after treatment with ASV that presents after 5–14 days of treatment. However, there is no specific definition to diagnose serum sickness or proven treatment. Here, we present a case of serum sickness to provide an insight into this unventured zone, briefing the presentation, treatment and probable reason for serum sickness and its prevention after common krait envenomation and treatment with polyvalent ASV in India.

Keywords: Emergency department, serum sickness, snakebite, snake venom

Introduction

Envenomation from snakebites is a significant public health concern in the Southeast Asian region resulting in considerable mortality and morbidity.[1,2] The World Health Organization has listed snakebites as a neglected tropical disease. Around 5 million snakebites are reported yearly, accounting for 81,000 to 1,38,000 deaths each year.[1] Anti-snake venom (ASV) remains the mainstay of treatment for snakebite envenomation.[3,4] ASV despite being the only rescue can bring forth several acute and delayed adverse effects. Among them, serum sickness is a late manifestation after treatment with ASV. It presents after 5–14 days of treatment.[3] There is no specific definition to diagnose serum sickness or proven treatment.[3] This case is an insight into this unventured zone, briefing the presentation, treatment and probable reason for serum sickness and its prevention after common krait envenomation and treatment with polyvalent ASV in India.

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Case Report

A male in his 60's (weight – 61 kg) presented to our emergency department (ED) with complaints of a common krait bite while walking near his farm at midnight. The bite was in the right gluteal region. He reported to the hospital at 5 AM with symptoms of dysphagia, ptosis and shortness of breath. His blood pressure was 80/45 mm Hg, heart rate was 130/minute, and respiratory

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rate was 28–30/minute. In view of cardiorespiratory failure, he was intubated and started on vasopressor support. Twenty vials of polyvalent ASV were given over 3 hours. His complete blood picture was normal, the 20-minute whole blood clotting test was normal, prothrombin time was 13.5 sec, the international normalized ratio (INR) was 1.2, and liver and renal function tests were within normal limits. This points towards a neurotoxic snakebite. The patient was mechanically ventilated for 36 hours. He was extubated after gaining good muscle strength and discharged after 3 days with good muscle power but with body aches.

After 6 days of discharge (9 days of snakebite), the patient presented to the ED with arthralgia of all major joints. Serum complement levels and C-reactive protein (CRP) were measured. The patient has no history of fever or exanthem. Thus, differentials, that is dengue fever, acute rheumatic fever, scarlet fever, IG-A vasculitis and Steven-Johnson syndrome, were ruled out. Complete blood picture was normal, and dengue serology was negative, thus negating dengue fever as the differential. The investigation revealed low complement levels (C3 levels – 1.46 mg/dl [normal value – 90–180]; C4 – 0.279 mg/dl [normal value – 10–40]) and raised CRP (1.6 gm/dl) value along with the history of ASV use and presentation of severe arthralgia points towards serum sickness. From the recent history of snakebite and the use of ASV with a decrease in complement levels and raise in CR*P* value, the diagnosis of serum sickness was confirmed.

The patient was treated with steroids (tablet prednisolone 60 mg OD for 1 week, followed by 30 mg for 1 week and 15 mg for 1 week and stopped) and antihistamines (tablet levocetirizine 5 mg OD for 1 week) considering it to be serum sickness. The severity of joint pains though decreased in intensity still persisted in this patient despite treatment. This could be suggestive of permanent damage to the joint capsule by the immune complexes.

Discussion

Serum sickness was first discovered by Clemens von Pirquet and Bela Schick in 1905 in patients injected with horse serum having antibodies against diphtheria. It presents between 5 and 14 days after administration of antivenom. The criteria to diagnose serum sickness vary with the type of antivenom and the geographical area. Incidence of serum sickness ranged from 5% to 56% in the United States based on the criteria included in the study. Various symptoms included in this study are fever, rash or urticaria, pruritus, arthralgia, myalgia, epigastric pain, thrombocytopenia and anorexia. However, to date, no consensus has been reached regarding the criteria to be considered to diagnose serum sickness after snake envenomation.[3,5] Adverse reactions to ASV, such as nausea, vomiting, chills, rigour and fever, have been mentioned in India, but the incidence of serum sickness was never been documented.[6]

The pathophysiology of serum sickness is controversial. The neutrophil and complement activation by the circulating immune complexes have been proposed as one of the reasons for serum sickness. Cellular receptors, such as C3bR, C5aR, and FcγIII, have been implicated as important components in this activation mechanism. The protein concentration in antivenom and its dose were proposed to be the other factors that could determine the onset of serum sickness but this was contradicted in a few studies.[7-9] Each 1 ml of ASV produced by Central Research Institute, Kasauli, India, can neutralize venoms of cobra 0.6 mg, common krait 0.45 mg, Russell's viper 0.6 mg and saw-scaled viper 0.45 mg. The ASV that we used is from VINS Bioproducts Limited [Figure 1]. It is an enzyme-refined sterile preparation of antiserum containing equine immunoglobulin fragments F (ab') 2.[10] As it is of equine origin, it is expected to mount all adverse reactions including serum sickness. Few authors defined serum sickness as a type 3 hypersensitivity reaction mounted by a large amount of circulating immune complexes after the use of ASV.[11] These immune complexes deposit in the blood vessel, kidney and joints if the macrophage system is malfunctioning and thus initiating hypersensitivity reaction leading to vasculitis, glomerulonephritis and arthritis, respectively. This occurs a week to 2 after the use of antivenom or may present even later when the patient is already sensitized. This deposition of immune complexes also activates the complement system erratically and lowers the complement levels (C3 and C4). The activated complement system causes the release of histamine, thus increasing the vascular permeability and mounting an inflammatory response. This process of clearing the complexes and targeted inflammatory response coincides with the onset of clinical symptoms. The presentation includes fever, rash and arthralgia of major joints. Less common features include lymphadenopathy, splenomegaly, anterior uveitis, headache or blurry vision, peripheral neuropathy, vasculitis and nephropathy. Based on the presentation, complete blood picture, renal and liver function parameters, complement levels (C3, C4 and CH50) levels, erythrocyte sedimentation rate (ESR), CRP, 2D echo in case of carditis and computerized tomography (CT) in case of neurological deficits are conducted. The patients usually manifest renal dysfunction, elevated CRP and ESR, and low complement levels.

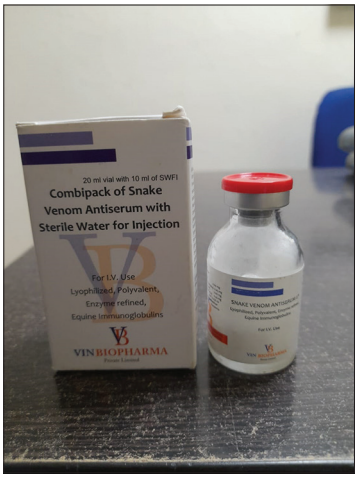

Figure 1: Figure depicting anti-snake venom used for the treatment

Various studies have proposed methods to prevent and treat serum sickness based on reasons attributed to its presentation. These include modifications in the preparation of antivenom, prophylactic use of adrenaline, hydrocortisone and promethazine which is not proven, and use of prednisolone when needed. The incidence and intensity of serum sickness can be decreased by decreasing the heterogeneity of antivenom and avoiding specific molecules, such as F (ab×), which have been mentioned as one of the molecules for the cause of serum sickness. Moreover, preference for humanized antibodies, ovine-based ASV and vaccination over anti-sera can address this problem at the earliest.[12,13] A Cochrane review stated that there is no proven role of corticosteroids in the prevention or treatment of late allergic reactions to antivenom.[3] However, mild to moderate cases of serum sickness are treated empirically with corticosteroids and antihistamines.[3] Severe cases are treated with adrenaline and prednisolone started at a dose of 60 mg/day (0.5–2 mg/kg), tapered off over 2 weeks based on the regression of the symptoms.[3] The patient needs to be educated regarding the adverse reaction on any further exposure. In a study conducted by Nicole M Ryan *et al.*,[9] the incidence of serum sickness with Australian ASV was reported to be 29% and the most common symptoms were fatigue, fever and muscle/joint pains. The ASV that we used was from an Indian manufacturer, and to our knowledge, no case report of serum sickness was reported after its use to date. However, a general note of caution has been mentioned. In a study conducted by Madhushani *et al.*,[14] the ability of VINS products, to prevent myotoxicity by Naja naja (king cobra) venom, was mentioned.

Conclusion

These cases are an insight into the presentation of serum sickness after the krait bite in India. ED physicians dealing with the management of snakebite cases should keep a high index of suspicion for serum sickness in patients administered ASV and presenting with delayed systemic symptoms. The patient still has joint pains even after treatment with steroids. Hence, more research is necessary to know the pathophysiology and thus improve the treatment necessary for serum sickness. The time at which steroids could be started and the role of immunotherapy in these cases need to be relooked at.

Consent

Written informed consent was obtained from the patient for the publication of this case report.

The authors attest that the article adheres to the standards of CARE reporting guidelines for case reports.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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