doi: 10.5216/rpt.v54i2.81822

CASE REPORT

PURPURA IN SERUM SICKNESS: A CASE OF POLYVALENT SNAKE ANTIVENOM REACTION FOLLOWING *Porthidium Ophryomegas* ENVENOMATION

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ABSTRACT

This reports a case of a 68-year-old woman with a history of snake bite from *Porthidium ophryomegas* (commonly known as Tamagás Negro), treated with polyvalent snake antivenom. The patient presents to the internal medicine service eight days after the snake bite, with generalized urticaria and palpable non-thrombocytopenic purpura. Based on her clinical history, she was diagnosed with serum sickness secondary to the snake antivenom, a potential complication of its administration. Serum sickness is caused by a type III hypersensitivity reaction, characterized by urticaria, fever, malaise, polyarthralgia, or polyarthritis, and less frequently, purpura secondary to allergic cutaneous vasculitis. There is no consensus regarding the diagnosis, which is clinical, based on medical history and suggestive symptomatology. This case was treated with corticosteroids, antihistamines, and topical antipruritic agents, resulting in the resolution of signs and symptoms without further complications. Although purpura is an uncommon manifestation of serum sickness, its occurrence following antivenom administration for snakebite should prompt consideration of this diagnosis.

KEY WORDS: Purpura; antivenom serum; snake bite; hypersensitivity; vasculitis.

INTRODUCTION

Snakebite envenomation is a potentially lethal condition due to the toxins of venomous snakes. It is estimated that snakebites cause between 81,000 and 138,000 deaths and 400,000 permanent disabilities each year (WHO, 2024). Despite its global significance, snakebites were not included in the World Health Organization's (WHO) list of priority neglected tropical

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Received for publication: 24/2/2025. Reviewed: 16/6/2025. Accepted: 24/6/2025.

diseases (NTDs) until 2017 (Fernández & Youssef, 2024). In Honduras, according to 2017 and 2018 data from the Honduran Epidemiological Bulletin, 750 cases were reported annually (Alger et al., 2019).

It must be taken into account that the massive entry into the organism of toxic agents such as snake venom does not allow an individual's immune system to develop a rapid and protective response. Based on this, the administration of antivenoms (passive immunization) constitutes the only specific alternative for the effective treatment of snake bites (Instituto Clodomiro Picado, 2016).

Snake antivenom can cause various acute and delayed adverse effects. Among these, serum sickness (SS) is a delayed adverse effect following its administration (Guru et al., 2024). SS is a type III hypersensitivity reaction mediated by the formation of antigen-antibody immune complexes that deposit in various tissues of the body, such as the microvasculature, joints, and lymph nodes, triggering an inflammatory response along with complement activation. Clinical manifestations typically emerge 1 to 3 weeks following exposure to the antivenom, presenting with cardinal signs such as rash, fever, polyarthralgia/ polyarthritis, and general malaise (Saad et al., 2016; Alangode et al., 2020; Meregildo-Rodriguez et al., 2020; Waiddyanatha et al., 2023; Guru et al., 2024).

Less frequently, purpura can occur as a manifestation of SS, pathophysiologically resulting from cutaneous leukocytoclastic vasculitis or hypersensitivity vasculitis (Saegeman et al., 2009; Pulido-Pérez et al., 2012; Sunderkötter et al., 2023). Leukocytoclastic vasculitis is a broad histopathological term referring to small-vessel cutaneous vasculitis, characterized by urticaria, plaques, papules, and palpable purpura. It is associated with infections, autoimmune disorders, certain medications, and as, in this case, SS (Strubchevska et al., 2023).

The objective of this report is to present a rare manifestation of serum sickness secondary to the use of polyvalent antivenom for a *Porthidium ophryomegas* snakebite.

CASE REPORT

A case is reported of a 68-year-old female patient from El Paraíso, Honduras, with a history of a snakebite to the right lower limb in the sub-malleolar area by a snake initially of unknown species, later confirmed by expert consultation as *P. ophryomegas*, commonly known in the region as Tamagás Negro. The study was approved by the Comité de Ética en Investigación Biomédica (CEIB) from the Facultad de Ciencias Médicas (IRB, number 00003070). The patient reports a history of arterial hypertension for over 20 years, controlled with irbesartan and hydrochlorothiazide. Upon admission, the patient presented with edema and pain in the affected limb,

leading to a diagnosis of grade II snakebite (localized edema and pain, without systemic envenomation).

Management included administration of polyvalent antivenom PoliVal-ICP® (anti-Bothropic, anti-Crotalic, anti-Lachesic) with a total of 15 vials due to persistent signs and symptoms. Additionally, tetanus immunoglobulin, analgesia with NSAIDs (Nonsteroidal Anti-Inflammatory Drugs), hydrocortisone, ranitidine, and antibiotic coverage with ceftriaxone 2 g intravenously (IV) daily and oxacillin 2 g IV every 6 hours were administered. The patient showed resolution of snakebite-related signs and symptoms and was discharged four days after admission without complications, with blood clotting tests, liver enzymes, and CBC (Complete Blood Count) within normal parameters. Outpatient management included dicloxacillin 500 mg orally every 6 hours and ibuprofen 600 mg orally every 8 hours for five days.

During hospitalization, the patient also reported chronic rectal bleeding. A digital rectal examination revealed mild rectorrhagia with dark blood, prompting the recommendation of further testing to investigate gastrointestinal bleeding.

The patient was readmitted to the internal medicine department eight days after the last dose of antivenom, presenting with a history of sudden-onset erythema and pruritus on the upper and lower limbs, as well as on the anterior and posterior thorax. One day later, she developed hives on her neck, back, and extremities, sparing the palms and soles, along with hot flashes and facial-eyelid edema. The patient also described non-pruritic, non-painful, pinpoint, violaceous lesions on her lower limbs.

The patient presents with the following vital signs: blood pressure 120/80 mmHg, heart rate and pulse 76 bpm, 19 breaths per minute, temperature 37.1 °C, and pulse oximetry at 98%. On physical examination, multiple polymorphic urticarial lesions were noted on the chest, abdomen, back, and upper limbs (Figure 1A). Additionally, palpable petechial purpura was observed on both lower limbs with a diffuse distribution, predominantly on the thighs, without hemorrhagic blisters, signs of cutaneous infections, or significant ecchymoses (Figure 1B and 1C). There were no clinical signs of sepsis or mucosal bleeding. Edema and erythema were evident in the limb affected by the snakebite, with a non-suppurative crusted lesion at the bite site (Figure 2).

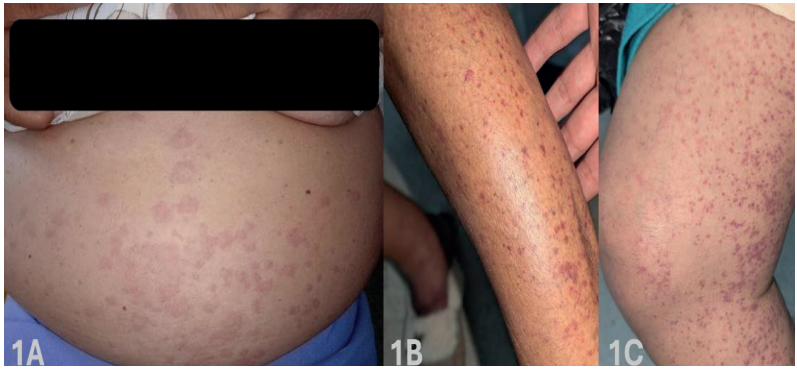

Figure 1. A) Multiple polymorphic urticarial lesions were found in the patient upon readmission. B and C) Palpable petechial purpura was found bilaterally on the lower extremities upon readmission.

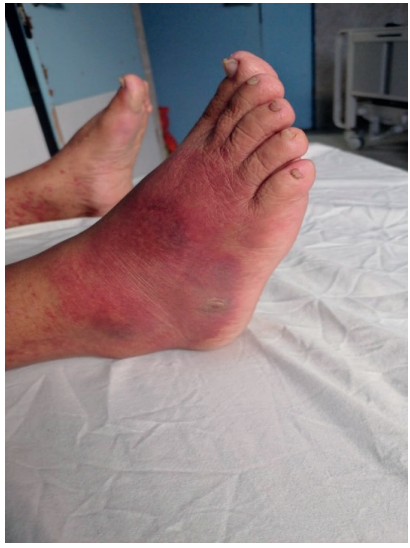

Figure 2. Edema and erythema are surrounded by purpura on the foot affected by the snakebite, with a non-suppurative crusted lesion at the bite site, eight days after the last dose of antivenom

Complementary tests were performed with the following results: complete blood count reports, including a white blood count (WBC) of 14,100/µL, Hb (Hemoglobin) of 11.9 g/dL, Hct (Hematocrit) of 35.8%, and platelets of 251,000/µL. The WBC differential count shows neutrophils at 77% (reference: 40–70%), lymphocytes at 13% (20–50%), monocytes at 5% (4–8%), and eosinophils at 5% (0–6%). A peripheral blood smear performed by a microbiologist reports normocytic normochromic red blood cells, with no blasts in the white cell series, and a platelet count confirmed by manual assessment. Coagulation times were reported as PT (Protrombin time) 13.4 seconds (reference: 12.7–15.4 s), aPTT (Activated Partial Thromboplastin Time) 31.4 seconds (26.3–39.4 s), and INR (International normalized ratio)1.03 (0.9–1.2). Blood chemistry results indicate glucose levels of 128 mg/dL, creatinine of 0.92 mg/dL, and BUN (Blood Urea Nitrogen) of 36.8 mg/dL, with a negative C-reactive protein result.

The urinalysis shows leukocyte esterase (++), blood (+) on chemical examination, with 9–12 leukocytes per field, scant bacteria, scant epithelial cells, and 1–2 erythrocytes per field on microscopic examination, with no proteinuria or casts in the urinary sediment.

Based on clinical findings and a history of antivenom administration, serum sickness was diagnosed, and the patient was admitted for further treatment. Differential diagnoses including anaphylaxis, dengue, sepsis, meningococcemia, thrombocytopenic purpura, and coagulopathies, were ruled out.

Upon admission, the patient was managed with dexamethasone 4 mg IV every 8 hours, diphenhydramine 50 mg IV every 8 hours, omeprazole 40 mg IV once daily, and topical calamine lotion applied three times daily. Antibiotic coverage with ceftriaxone 1 gram IV every 12 hours and clindamycin 300 mg IV every 8 hours was initiated due to inflammatory changes at the snakebite site. This antibiotic coverage was discontinued after 48 hours, as no signs of local infection were observed.

The patient demonstrated clinical improvement during her 4-day hospital stay, with the resolution of cutaneous lesions and no evidence of additional complications. Outpatient management included oral prednisone starting at 50 mg daily, with a gradual taper of 5 mg every three days until reaching 10 mg, at which point the steroid was discontinued. Loratadine 10 mg orally once daily was also prescribed until symptom resolution.

A follow-up was conducted via telephone, confirming a complete resolution of the disease. It is noteworthy that the patient continued undergoing complementary studies for gastrointestinal bleeding, with a subsequent diagnosis of colon cancer via colonoscopy.

DISCUSSION

Serum sickness (SS) is a type III hypersensitivity reaction, with proposed mechanisms that suggest the formation of antigen-antibody immune complexes mediates it, although its pathophysiology remains controversial. These complexes deposit in various tissues, including the body's microvasculature, joints, and lymph nodes, triggering an inflammatory response through the activation of the neutrophil and complement systems via C3bR, C5aR, and FcγIII cellular receptors (Guru et al., 2024).

Between 5.6% and 29% of patients develop SS following the administration of snake antivenom serum. The development of SS has also been reported with other substances, including antivenoms against arachnid envenomation, microbial antitoxins (for diphtheria, rabies, botulism), monoclonal antibodies and immunomodulators (infliximab, rituximab, antithymocyte globulin, etc), fibrinolytic proteins (streptokinase), among others (Meregildo-Rodriguez et al., 2020).

This results in the appearance of classic symptoms 1–3 weeks after drug administration, or sooner in cases of re-exposure to the same antigen. These symptoms include rash, fever, general malaise, polyarthralgia/ polyarthritis, and, less frequently, headache, edema, lymphadenopathy, splenomegaly, blurred vision, glomerulonephritis, gastrointestinal symptoms, and peripheral neuropathy (Ryan et al., 2015; Saad et al., 2016). Purpura secondary to hypersensitivity vasculitis or leukocytoclastic vasculitis is an uncommon presentation and is rarely reported in the medical literature (Karmacharya et al., 2015; Ryan et al., 2015; Instituto Clodomiro Picado, 2016; Saad et al., 2016; Alangode et al., 2020; Guru et al., 2024).

In our case, the patient did not exhibit the classic symptoms of fever or polyarthralgia/ polyarthritis; however, she did present with urticaria, edema, and purpura predominantly on the lower limbs, along with a clinical history of antivenom administration and the onset of symptoms within the 1–3-week range following its use.

There is no consensus regarding the diagnosis, nor are there laboratory tests that aid in establishing it; thus, it is based on signs and symptoms alongside the clinical history of antivenom administration (Saad et al., 2016; Alhawal et al., 2021). This represents a limitation when comparing SS incidence results across studies, highlighting the need for criteria to enable better characterization (Ryan et al., 2016).

Laboratory findings are variable and may include neutropenia or leukocytosis, thrombocytopenia, eosinophilia, elevated ESR (Erythrocyte Sedimentation Rate) and CRP (C- reactive protein), mild proteinuria, hematuria, and hypocomplementemia (C3, C4, CH50) (Ryan et al., 2015; Alhawal et al., 2021). The patient in this case exhibited leukocytosis with neutrophilia, lymphopenia, mild anemia, no thrombocytopenia, standard coagulation tests,

negative CRP, regular renal function tests, leukocyturia, and blood in urine (+) without other urinary sediment abnormalities. The mild anemia could be attributed to the colon cancer diagnosed after the patient's discharge.

The prognosis for SS is generally favorable and typically resolves within 1–2 weeks if the causative agent is discontinued (Shrestha et al., 2024). Treatment recommendations vary, with antihistamines and NSAIDs used for mild disease, and corticosteroids for severe disease or systemic manifestations, such as vasculitis, severe arthritis, or persistent high fever (Instituto Clodomiro Picado, 2016; Ryan et al., 2016; Saad et al., 2016). Some authors propose a diagnostic and therapeutic trial with oral prednisone at 40–60 mg/day, tapered over two weeks (Clark et al., 2006).

Our patient showed favorable clinical response to the prescribed management, including antihistamines, topical antipruritic (calamine), and corticosteroids with dexamethasone 4 mg IV every 8 hours for 4 days during hospitalization, followed by oral prednisone at 50 mg daily, tapered by 5 mg every 3 days until discontinuation at 10 mg, for a total of 28 days.

Upon readmission, the patient explicitly denied the use of any new medications, herbal supplements, or exposure to other potential allergens or infectious agents that could account for her symptoms. This absence of alternative triggers strengthens the causal relationship between the antivenom administration and the development of serum sickness.

This case report had certain limitations, including the absence of a skin biopsy of the purpuric lesions, which would have definitively identified the histological patterns of leukocytoclastic vasculitis. Due to this, it is suspected that leukocytoclastic vasculitis is the cause of the palpable non-thrombocytopenic purpura exhibited by the patient. However, since SS is a clinical diagnosis, a skin biopsy is not strictly necessary. Additionally, it was not possible to determine the complement system values in the patient due to the unavailability of this test at the regional basic hospital to which the patient presented.

Another unresolved question is whether the patient's colon cancer might have an immunological mechanism predisposing her to this hypersensitivity reaction, although this is beyond the scope of this study.

Serum sickness is a clinical diagnosis, supported by laboratory findings, clinical history, and the characteristic self-limiting nature of the disease, which typically responds well to corticosteroids. It is important to consider this possible type III hypersensitivity complication, as well as the rare presentation of purpura, in the context of antivenom administration.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest to disclose.

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