European Journal of Clinical and Experimental Medicine

ONLINE FIRST

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Article type: Case Report

Received: 25 May 2026

Accepted: 20 July 2026

Published online: 28 July 2026

eISSN: 2544-1361

Eur J Clin Exp Med

doi:10.15584/ejcem.2026.3.10

Anaphylaxis to antivenom in the background of alpha-gal syndrome – a case report

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ABSTRACT

Introduction and aim. Alpha-gal syndrome is an IgE-mediated allergy to galactose-α-1,3-galactose, typically associated with delayed hypersensitivity reactions following ingestion of mammalian meat. Severe immediate hypersensitivity reactions to equine-derived antivenom in patients with previously unrecognized alpha-gal syndrome are rarely reported. We report one of the first cases from South Asia of refractory anaphylaxis following equine-derived antivenom in a patient with previously undiagnosed alpha-gal syndrome, highlighting an important but under-recognized clinical challenge.

Description of the case. A 45-year-old Sri Lankan woman developed refractory anaphylaxis shortly after administration of equine-derived antivenom for a Russell's viper bite. She required intravenous adrenaline and noradrenaline infusions, fluid resuscitation, and high-dependency care, with subsequent full recovery. Further evaluation revealed a history suggestive of alpha-gal syndrome, including recurrent urticaria and wheezing following consumption of mammalian meat and dairy products, as well as possible anaphylaxis to wasp stings. Serum alpha-gal–specific IgE levels were markedly elevated.

Conclusion. This case highlights the potential for severe hypersensitivity reactions to mammalian-derived antivenoms in patients with alpha-gal syndrome.

Keywords. alpha-gal syndrome, anaphylaxis, antivenom hypersensitivity

Introduction

Alpha-gal syndrome (AGS), an immunoglobulin E (IgE) mediated allergy to the oligosaccharide galactose-α-1,3-galactose (alpha-gal), classically presents with delayed urticaria, angioedema, or anaphylaxis following ingestion of mammalian meat or meat-derived products.[1] This condition is commonly associated with sensitization triggered by bites from certain hard ticks, particularly *Amblyomma americanum* in the USA. A unique and evolving facet of this syndrome is the recognition of anaphylactic reactions to medications and biologics that contain mammalian-derived glycoproteins.[2] However, evidence linking AGS to hypersensitivity reactions following equine-derived antivenom remains limited, with only a few cases reported worldwide and very little published experience from South Asia, where snakebite is a major public health problem.

Aim

We report this case to highlight a biologically plausible association between previously unrecognized AGS and severe immediate hypersensitivity following equine-derived antivenom, and to increase clinical awareness of this rare but potentially life-threatening complication in regions where snakebite and alpha-gal syndrome may coexist.

Description of the case

A 45-year-old female presented 30 minutes after sustaining a Russell's viper (*Daboia russelii*) bite to her left big toe. The incident occurred while she was gardening at home. The dead specimen was brought to the hospital and identified by the medical officer. On admission, she complained of severe local pain, vomiting, shortness of breath, and wheezing (Table 1). She was drowsy, with a blood pressure of 150/80 mmHg, a pulse rate of 80 beats per minute, and bilateral widespread rhonchi on lung auscultation. Examination of the bite site revealed two distinct fang marks, local bleeding, and tenderness, but no oedema. The 20-minute whole blood clotting test was noncoagulopathic (Table 2).

In view of having a non-specific systemic envenomation feature (vomiting), along with the positively identified snake specimen, 20 vials of Indian polyvalent antivenom serum (Bharat SV Ltd, manufactured in 12/2024, lot number 18224078) were administered 60 minutes after the bite at the emergency treatment unit, following the national guideline for snakebite management. Subcutaneous Adrenaline 1:1000 dilution (0.25 mg) was given as premedication. Within five minutes of starting antivenom serum, the patient developed acute worsening of dyspnea and wheezing, accompanied by faintness and hypotension (blood pressure, 70/40 mmHg, pulse oximeter oxygen saturation 94%). Anaphylaxis to antivenom was diagnosed and was treated immediately with three intramuscular doses of adrenaline 1:1000 dilution, 0.5 mg. As hypotension persisted with features of shock, the reaction was classified as refractory anaphylaxis, and she

was commenced on intravenous adrenaline 0.1 µg/kg/minute and noradrenaline infusion at 0.4 µg/kg/minute. Antivenom administration was completed with vasopressor support within 60 minutes. Additional management included fluid resuscitation and nebulized bronchodilators. Following antivenom administration and anaphylaxis management, her respiratory distress resolved, with clear lung fields on auscultation.

Following stabilization, the patient was transferred to the medical casualty ward four hours after admission and subsequently managed in the high dependency unit. She made a full recovery and was discharged after four days of inpatient care. The patient had no evidence of developing venom-induced consumption coagulopathy with a normal international normalized ratio (Table 2), neuromuscular paralysis or acute kidney injury.

Table 1. Timeline of clinical presentation, therapeutic interventions, and patient outcomes following Russell's viper envenomation and antivenom-induced anaphylaxis

Time elapsed	Clinical event and intervention	Clinical status and key metrics
0 minutes	Russell's viper bite to left big toe while gardening at home.	Dead specimen brought for identification.
30 minutes	Admission to emergency department. Dead snake positively identified as *Daboia russelii*.	Drowsy, severe local pain, vomiting, dyspnea, wheezing. BP: 150/80 mmHg, PR: 80 bpm. Lungs: Bilateral widespread rhonchi. 20-WBCT: Noncoagulopathic.
60 minutes	Premedication and antivenom initiation. Given 0.25 mg subcutaneous adrenaline. Started infusion of 20 vials of Indian polyvalent antivenom serum.	Non-specific systemic features (vomiting).
65 minutes	Severe anaphylaxis onset. Antivenom halted. Treated with 3 doses of IM adrenaline 0.5 mg. Classified as refractory anaphylaxis; initiated IV adrenaline and noradrenaline infusions.	Acute worsening of dyspnea, wheezing, faintness, and shock. BP: 70/40 mmHg, SpO_2:94%.
120 minutes	20 vials of antivenom administered under continuous vasopressor and inotropic support.	Stabilization achieved. Respiratory distress resolved; lung fields clear on auscultation.

4 hours	Patient stabilized and transferred to the medical casualty ward.	Hemodynamically stable.
Days 1–3	Inpatient monitoring. Serial testing performed.	No evidence of VICC, neuromuscular paralysis, or acute kidney injury.
Day 4	Discharge home.	

The patient reported a previous episode of possible anaphylaxis to a wasp sting four years earlier. Over the past five years, she had experienced recurrent urticarial rashes and wheezing following ingestion of mammalian meat and milk products.

There was a strong family history of allergic disorders and anaphylaxis. Her mother died at approximately 60 years of age following a possible anaphylactic reaction to wasp stings. Her elder sister suffers from urticaria triggered by fish, meat, insect bites, and even water exposure. Additionally, the elder sister's two daughters also experience urticarial reactions following insect bites. Notably, male family members are unaffected. Assessment of physical urticaria subtypes revealed dermatographia in both the patient and her sister. The sister additionally demonstrated aquagenic and cold urticaria, while other subtypes (cholinergic, delayed pressure, vibratory, solar, and exercise-induced) were absent in both individuals.

Serum testing revealed a markedly elevated alpha-gal–specific IgE level of 17.1 kUA/L (immunoCAP class 3, high positive: 3.50–17.49 kUA/L), supporting the diagnosis of alpha-gal syndrome. This was performed using the allergen-specific IgE fluorescent enzyme immunoassay (Phadia ImmunoCap, Phadia 100). Her total IgE level was 468.3 IU/L, with an alpha-gal–specific IgE-to-total IgE ratio of 3.6%, which is associated with a high likelihood of clinically significant meat allergy. There is no universally accepted reference range for the ratio.[3] However, these values are considered clinically meaningful for risk stratification and diagnostic purposes.[3,4] Serum tryptase was not measured due to unavailability.

Table 2. Laboratory investigations performed during hospitalization*

Investigations	**Reference range**	**Day 1**	**Day 3**
White cell count	4–10 $\times 10^9$/L	14.53	12.49
Neutrophils	50–70%	95.3	90.6
Lymphocytes	20–40%	2.3	8.1
Eosinophils	1.0–6.0%	0.0	0.0
Haemoglobin	11–17 g/dL	11.4	11.8
Platelets	150–400 $\times 10^9$/L	347	380
Blood urea	2.8–7.7 mmol/L	4.8	NR
Serum creatinine	60–120 µmol/L	94	84

Sodium	135–148 mmol/L	146	146
Potassium	3.6–5.0 mmol/L	3.2	4.1
C-reactive protein	<5 mg/L	3.99	NR
Prothrombin time	12.3–16.3 s	15.9	16.3
International normalised ratio	<1.5	1.13	0.92
Activated partial thromboplastin time	25–38 s	22.8	NR
Urine full report	protein trace; pus cells 10–12/HPF; red cells 50–60/HPF		
Blood picture	reactive changes due to inflammation, no evidence of microangiopathic hemolytic anemia		

* NR – not repeated, HPF – high power field

Discussion

Refractory anaphylaxis developed immediately after antivenom administration in this patient, requiring dual vasopressor support. The temporal relationship between antivenom administration and the onset of anaphylaxis, together with markedly elevated alpha-gal-specific IgE levels, suggests a biologically plausible association between underlying alpha-gal sensitization and severe immediate hypersensitivity following equine-derived antivenom. However, in the absence of definitive immunological confirmation, a causal relationship cannot be established. While similar reactions have been reported previously, this case adds to the limited literature by describing severe refractory anaphylaxis following Russell's viper antivenom in South Asia, in a patient with previously unrecognized alpha-gal syndrome and a female-predominant familial clustering of allergic manifestations. The case also highlights the diagnostic and therapeutic challenges encountered in resource-limited emergency settings.

Previous reports have described immediate hypersensitivity reactions to equine-derived antivenom in patients with alpha-gal syndrome and have demonstrated that alpha-gal epitopes present on equine $F(ab')_2$ antivenoms can trigger IgE-mediated reactions.[10,13,16] However, published cases remain few, and most originate from North America or Europe. In contrast, our patient developed refractory anaphylaxis following Indian polyvalent Russell's viper antivenom in the setting of previously unrecognized alpha-gal syndrome in South Asia. This case therefore extends the existing literature by illustrating the relevance of alpha-gal syndrome in a region where snakebite is common, and access to specialized allergy investigations is limited.

Hard tick species (Ixodidae), recognized as vectors associated with alpha-gal syndrome in other regions, are present in Sri Lanka. Recent evidence also supports the occurrence of alpha-gal syndrome in Sri Lanka, with Amblyomma testudinarium proposed as a possible vector.[5,6] This case underscores an underrecognized

risk in snakebite management in tick-endemic regions, where alpha-gal syndrome may be prevalent yet largely undiagnosed. Alpha-gal syndrome is an IgE-mediated allergy to galactose-α-1,3-galactose, classically associated with delayed reactions after mammalian meat ingestion, whereas intravenous exposure to alpha-gal–containing products can trigger immediate anaphylaxis.[7,8]

Some snake venoms contain terminal alpha-galactosyl residues, such as those from some cobra species (genus *Naja*) .[9] However, whether Russell's viper venom contains this epitope is yet unknown. Antivenoms derived from mammalian serum, such as horse serum, contain the galactose-α-1,3-galactose (alpha-gal) epitope, which is a known target of IgE-mediated hypersensitivity in patients with alpha-gal syndrome. Pepsin digestion removes the Fc portion but does not eliminate N-linked glycans on Fab fragments that carry the alpha-gal epitope. This epitope binds pre-existing human anti-alpha-gal IgE, triggering basophil activation and anaphylaxis, with higher reaction rates observed in $F(ab')_2$ antivenom compared to Fab products.[10,11] Researchers have identified the alpha-gal epitope as a target of IgE-mediated reactivity in equine antivenoms, thereby explaining how individuals with alpha-gal syndrome can experience immediate anaphylaxis upon first administration. Consequently, the presence of these epitopes in Indian polyvalent antivenom is a biologically plausible cause of such reactions in sensitized patients, as this specific antivenom (Bharath SV Ltd) has been confirmed to contain alpha-gal and elicit high levels of basophil activation in clinical studies. However, it is noteworthy that conflicting findings have been reported, with specific IgE against α-gal not being a major trigger of early anaphylactic reactions in Laotian snakebite patients who received Thai antivenom.[12,13]

Familial clustering and emerging data on intrinsic host risk factors (including non–B-antigen ABO blood groups and a family history of alpha-gal or other allergies) suggest that, beyond tick exposure alone, some individuals may have an underlying susceptibility to the clinical manifestations of alpha-gal syndrome.[14] Hereditary α-tryptasaemia is a well-described familial trait that increases baseline tryptase and can amplify anaphylaxis risk and severity, so it is a biologically plausible contributor to multigenerational clustering of severe reactions; it does not replace tick exposure as the main driver of α-gal IgE sensitisation.[15]

The management of snakebite in a patient with alpha-gal syndrome creates a therapeutic dilemma. The standard of care, the administration of polyclonal antivenom derived from horse serum, carries a high alpha-gal load and poses a risk of anaphylaxis.[16] Pre-medication protocols, graded challenge, or consideration of novel, low-IgE antivenoms are options for preventing such complications.[16,17]

This case has several limitations. First, the indication for antivenom administration was not unequivocal, as the patient did not develop definitive evidence of systemic envenomation such as coagulopathy, neurotoxicity, or progressive systemic manifestations beyond persistent vomiting. This represents an important clinical consideration, as unnecessary antivenom exposure may increase the risk of severe hypersensitivity reactions. Although snake venom itself may have contributed to the allergic reaction, the anaphylactic episode occurred shortly after antivenom administration, making antivenom the more likely

trigger. Furthermore, several specialized investigations were unavailable, including serial serum tryptase measurements, antivenom-specific IgE assays, and basophil activation testing. Therefore, although alpha-gal syndrome is biologically plausible, definitive immunological confirmation could not be established. In addition, serial follow-up measurements of alpha-gal-specific IgE were unavailable; therefore, changes in sensitization over time following avoidance of mammalian products and subsequent tick exposure could not be assessed.

Patient's perspective

This patient was concerned about her medical condition, as she had lost her mother due to an anaphylactic reaction, and she was also having similar reactions. Therefore, she wants to know how to prevent recurrences, what other tests are available to aid in diagnosis, and what treatment options are available. She was happy with our diagnosis and the instructions, and she and her family members will be more cautious about future exposures that could trigger additional allergic reactions.

Conclusion

A high index of clinical suspicion for alpha-gal syndrome is needed in patients presenting with unexplained anaphylaxis, recurrent reactions to insect stings, mammalian meat allergy, or severe reactions to biologic products, including antivenom. An important clinical learning point from this case is that the indication for antivenom administration was not unequivocal, as the patient did not develop objective evidence of systemic envenomation such as coagulopathy, neurotoxicity, or progressive systemic manifestations beyond persistent vomiting. This highlights the importance of assessing the risk-benefit balance before administering antivenom, particularly in patients with a history suggestive of severe allergic disease. Future studies are warranted to determine whether routine risk assessment or alternative antivenom strategies could improve patient safety.

Declarations

Funding

The authors declared no financial support.

Author contributions

Conceptualization, A.S., D.L. and S.S.; Methodology, D.L. and A.S.; Validation, M.R. and S.W.; Formal Analysis, S.W. and S.S.; Investigation, S.W. and M.R.; Resources, S.S.; Data Curation, D.L., M.R. and S.S.; Writing – Original Draft Preparation, D.L.; Writing – Review & Editing, D.L., M.R., S.W., A.S. and S.S.; Visualization M.R.; Supervision, A.S. and S.S.; Project Administration, S.S.

Conflicts of interest

The authors declare no conflicts of interest.

Data availability

The data that support the findings of this study are available from the corresponding author upon request.

Ethics approval

Patient's consent was obtained for the publication of this case report and accompanying clinical details. Written informed consent for publication was obtained from the patient in Sinhala, the local language. The signed consent form is uploaded as a supplementary document. This is a single case report. Formal ethics committee approval was not required under institutional policy; patient consent for publication was obtained as noted above.

Use of AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used Vera Health & ChatGPT only to check for errors and perform proofreading in some parts of the manuscript. After using this tool/service, the authors reviewed and edited the content as needed and took full responsibility for the published article.

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