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Urticarial Rash in a Patient with Alpha-Gal Syndrome Caused by Subcutaneous Heparin at Prophylactic Dosing: A Case Report

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CASE REPORT

Urticarial Rash in a Patient with Alpha-Gal Syndrome Caused by Subcutaneous Heparin at Prophylactic Dosing: A Case Report

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Introduction: We report a patient with a history of red meat allergy, or alpha-gal syndrome, who had an urticarial rash after exposure to unfractionated heparin at a dose typically used for prophylaxis of deep venous thrombosis. Although anaphylactic reactions have been reported with systemic intravenous heparin, we believe this case is the first report of an immunoglobulin E–mediated reaction to subcutaneous heparin at prophylactic dosing.

Clinical Findings: An 85-year-old male had a 3-year history of red meat allergy and was intolerant of pork and beef. He developed an immunoglobulin E–mediated allergic reaction to subcutaneous heparin at a dose of 5000 units twice daily.

Clinical Course: The patient presented to the emergency department after a fall. He had back pain and was diagnosed with a compression fracture. He was admitted to the hospital because he was unable to safely ambulate. He was treated with subcutaneous unfractionated heparin to prevent deep venous thrombosis as part of routine care. Twenty-four hours after exposure to heparin, he developed an urticarial rash. The rash resolved promptly after discontinuing heparin and excluding other potential allergic triggers.

Conclusions: In patients with alpha-gal syndrome, unfractionated heparin via a subcutaneous route at prophylactic dosing can precipitate immunoglobulin E–mediated systemic reactions and should be avoided.

Keywords: red meat allergy, heparin, food hypersensitivity, urticaria, alpha-gal syndrome

An 85-year-old male was admitted to the hospital for a vertebral compression fracture. His past medical history included coronary artery disease and atrial fibrillation treated with rivaroxaban. Three years prior, he developed hives, nausea, vomiting, and diarrhea after eating beef and pork. At that time, he reported occupational exposure to ticks as a cattle farmer and no recent travel. A lone star tick bite was presumed from occupational exposure. At that time, he had serologic evidence of allergy to galactose alpha-1,3-galactose (alpha-gal), with an alpha-gal IgE titer of 85.8 kU/L, and was diagnosed with alpha-gal syndrome.

At admission, rivaroxaban was discontinued in favor of aspirin and clopidogrel. On hospital day 4, he was given subcutaneous heparin at 5000 units twice daily for deep vein thrombosis (DVT) prophylaxis. On hospital day 5, he developed hives and was given cetirizine. On hospital day 6, his rash worsened. Dermatology confirmed urticaria without angioedema. The most likely etiology was a medication allergy, likely due to heparin, aspirin, or clopidogrel. The patient's wife reported that the rash appeared similar to when he consumed meat. Staff had been attentive to his dietary intake and reported no exposure to dietary pork or beef. Aspirin and clopidogrel were continued, and heparin was discontinued on hospital day 7. The patient received a total of 7 doses of 5000 units subcutaneous heparin. Figure 1 shows the appearance of the rash on hospital day 9. The rash was improving on hospital day 10 and had resolved by hospital day 13 (Figure 2).

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Figure 1. Urticarial Rash Developed in the Patient on Hospital Day 9, After Exposure to Subcutaneous Heparin



Figure 2. Urticarial Rash Improved in the Patient on Hospital Day 13, After Stopping Heparin Administration

DISCUSSION

Alpha-gal syndrome is caused by immunoglobulin E (IgE) antibodies to galactose alpha-1,3-galactose, a surface mono-oligosaccharide found in non-primate mammals.¹ Alpha-gal syndrome often clinically manifests as delayed anaphylaxis 3 to 6 hours after red meat ingestion and develops after tick bite, usually by the lone star tick (*Amblyomma americanum*) in the United States.² These tick bites are theorized to cause basophil, eosinophil, and type-2 cytokine-producing T-cell infiltration, which results in production of alpha-gal IgE antibody via signaling pathways involving myeloid differentiation factor 88.^{3,4}

Although meat intolerance is the most consistent manifestation, alpha-gal is also present at varying small amounts in medications, which may cause IgE-mediated reactions in patients who are allergic to alpha-gal after exposure to one of these medications. In fact, alpha-gal allergy was initially discovered after systemic reactions to cetuximab, which contains an alpha-gal component, proving alpha-gal reactivity in the bloodstream as well as the gastrointestinal tract.⁵ Heparin is derived from bovine lung tissue and porcine intestine tissue, and it may contain variable amounts of alpha-gal depending on the lot number and manufacturer.¹

Reports have described anaphylactic reactions to systemic heparin in patients with alpha-gal allergy. These reactions seem to directly correlate with alpha-gal allergy, including significantly higher alpha-gal IgE titers in patients with reactions during cardiovascular surgery.¹ However, previous reports describe intravenous administration and higher doses of heparin used for cardiopulmonary bypass^{1, 6-8} or a left-ventricular assist device.⁹ Our patient was exposed to a lower dose of heparin via a subcutaneous route. In our literature review, we did not find any reported cases of allergic reaction to subcutaneous heparin in a patient with alpha-gal syndrome. Some studies reported tolerance of subcutaneous dosing in patients who reacted to parenteral doses during cardiac surgery.^{1,6}

In addition to the lower dose and novel route of administration, our patient resided in Northern New England. Alpha-gal syndrome was initially recognized around 2006. At this time, the incidence of anaphylactic reactions following infusion of the alpha-gal-containing medication cetuximab increased in patients with cancer living in the Southeastern United States. In 2006, the range of the lone star tick was limited to the Southeastern United States, leading to a causal link between the lone star tick bite and alpha-gal sensitization.⁵ In the past 15 years, however, the range of the lone star tick has expanded and now includes most

of Maine.¹³ Because this range has only recently expanded to Northern New England, medical providers in this area may be less aware of alpha-gal syndrome.

In the context of a cardiac emergency, desensitization, pre-medication, or alternative medications (bivalirudin, cangrelor) may be considered and have been tested successfully.^{7, 8-11} However, considering the low risk of DVT and the clear risk of anaphylactic reaction or severe non-anaphylactic reaction, as in our patient, we suggest avoiding all heparin products in patients with alpha-gal syndrome for DVT prophylactic dosing. Non-heparinoid products, such as fondaparinux, should be equally effective and carry no risk of allergic reactions to alpha-gal. This advice may be prudent for other medications thought to contain alpha-gal that have reasonable alternatives, including opioids, acetaminophen, pregabalin, and haloperidol.¹² Ultimately, we hope to spark further research into the reactivity and safety of subcutaneous heparin in patients with alpha-gal syndrome.

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