Case Presentation

Reactive angioendotheliomatosis as a side effect of long-acting injectable insulin use

Kennedy Stoll, MS[1], Samantha Holmes Seward, MD[1], Terrence M Katona, DO[1], Sahand Rahnama-Moghadam, MD, MS[1a]

[1] Indiana University School of Medicine, Department of Dermatology, Indianapolis, Indiana, United States

Keywords: angioendotheliomatosis, injection, insulin, trauma

Dermatology Online Journal

Vol. 31, Issue 4, 2025

Abstract

A 44-year-old woman with type II diabetes mellitus presented with an 8-month history of a painful, ulcerating rash at the area of insulin injection of her left lower abdomen. Topical antibiotics, topical corticosteroids, oral antibiotics, and supportive wound care provided no relief. A similar eruption developed on the right abdomen when she switched injection sites. Wedge biopsy of the violaceous, reticular plaque demonstrated a central dermal scar with surrounding lobular and linear collections of small blood vessels, consistent with reactive angioendotheliomatosis. This condition typically occurs secondary to an underlying systemic disease, but we believe hers was a side effect related to trauma from insulin injection or secondary to insulin additive hypersensitivity. The patient was switched to a glucagon-like peptide-1 agonist, active lesions were treated with topical timolol 0.5% ophthalmic solution, and oral propranolol was started with upward titration. She continues to see improvement in pain and has not developed any new ulceration at other sites on the body.

Introduction

Angiotheliomatosis is classified under the umbrella terminology of cutaneous reactive angiomatosis, making it one of three major subtypes.[1] It is then further separated into reactive and malignant entities, the latter of which includes either Kaposi sarcoma or angiosarcoma.[2] Reactive angioendotheliomatosis (RAE) is a relatively rare phenomenon not well described with the literature, consisting largely of case reports.[3] This condition is characterized by intravascular proliferation of endothelial cells and is often seen in the setting of systemic diseases such as infection, immunosuppression, cryoglobulinemia, lymphoproliferative disorders, autoimmune disorders, antiphospholipid syndrome, and peripheral vascular disease.[1,3]

Case Synopsis

A 44-year-old woman with past medical history of insulin-dependent type II diabetes mellitus, presented with an 8-month history of a painful, ulcerating rash on the left lower abdomen. Her condition was refractory to trials of topical antibiotics, topical corticosteroids, oral antibiotics, and supportive wound care. Interestingly, the patient reported history of injecting her long-acting insulin in this area.

Furthermore, when the patient switched injections sites to the right abdomen, she developed a similar eruption. She had no history of autoimmune disorders, blood clots, or new medications.

Physical examination revealed violaceous, reticular or retiform appearing plaques with areas of atrophic white scarring and ulceration on the left lateral lower abdomen (Figure 1). Autoimmune panel, hypercoagulability workup, complete blood count (CBC), comprehensive metabolic panel (CMP), and glycosylated hemoglobin (A1C) were within normal limits or negative. A wedge incisional biopsy was obtained for confirmation of diagnosis (Figure 2).

Histopathology demonstrated a central dermal scar with adjacent/surrounding lobular and linear collections of capillaries and small blood vessels. An infarct was not identified. Changes of calciphylaxis, vasculitis, or intravascular thrombi were not identified. Panniculitis was not present, and very focal fat necrosis was found at one tip of the biopsy. There was also background mild, superficial and mid dermal perivascular lymphoplasmacytic inflammation.

a Corresponding Author: Sahand Rahnama-Moghadam MD MS, 545 Barnhill Drive, Emerson Hall 139, Indianapolis, IN 46202, Tel: 317-944-7744, Email: srahnama@iu.edu

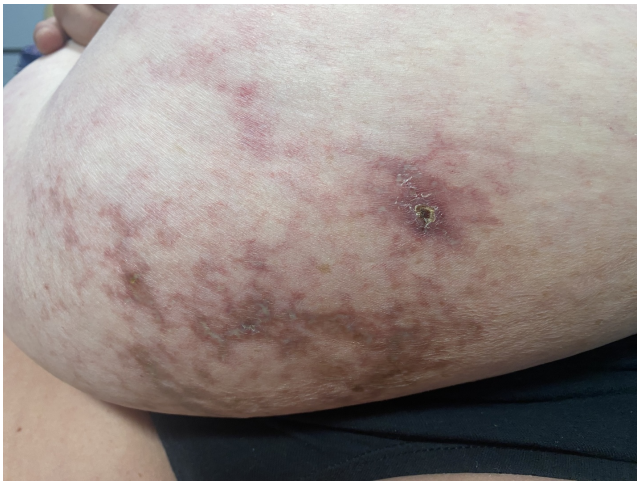

Figure 1. *Clinical photograph of the left lateral lower abdomen showing retiform erythema and purpura with ulceration.*

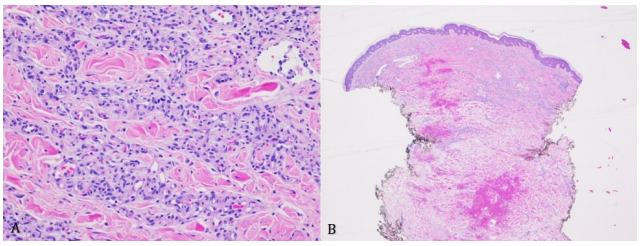

Figure 2. *Photomicrograph from tip portion of serially sectioned wedge incisional biopsy featuring central dermal scar with adjacent/surrounding lobular and linear collections of capillaries and small blood vessels lined by a single layer of cytologically bland endothelial cells. Hematoxylin-eosin-stained sections with original magnification at **A)** 200x and **B)** 20x.*

Discussion

Reactive angioendotheliomatosis presents as erythematous macules, purpuric papules, ecchymoses, or purpuric plaques, which may ulcerate or become necrotic.[1,3] Although commonly present on the extremities, it rarely manifests on the head and neck.[2] Our patient had a classic violaceous plaque with ulceration in an atypical location. Diffuse dermal angiomatosis, and acroangiodermatitis, the two other major subtypes of cutaneous reactive angiomatosis, can also present with ulcerating plaques so histologic evaluation is necessary for differentiation.[2,3] Reactive angioendotheliomatosis pathophysiology is unclear, but systemic or localized hypoxia most likely plays a role. This hypothesis corresponds with the frequent presentation in individuals who have systemic conditions that predispose to vascular occlusion or inflammation.[1] Although some lesions may resolve on their own, others necessitate treatments aimed at reducing hypoxia and addressing underlying conditions.[3]

At least one case report described post-traumatic reactive angioendotheliomatosis in an otherwise healthy individual after a traffic collision.[1] Our patient had no history of underlying autoimmune disease and laboratory workup was largely within normal limits. Therefore, we believe her RAE was either post-traumatic related to the act of injecting insulin in the abdomen or secondary to an insulin additive hypersensitivity. There are several reports of patients using human insulin developing various allergic reactions ranging from erythema to anaphylaxis. These allergic reactions can be related to the insulin protein itself or non-medicinal excipients and preservatives, such as glycerol, dibasic sodium phosphate, zinc, or the phenol family including o-cresol and m-cresol.[4,5] These excipients are found in nearly all insulin formulations and added to maintain sterility of the solution and aid in stabilization.[5]

As the overall prognosis for RAE appears good with disease being self-limited in most cases, there is no standard treatment.[1,3] After discussion with a clinical pharmacist and the patient's primary care provider about our concerns for possible insulin protein or excipient hypersensitivity, the decision was made to switch the patient from m-cresol containing insulin glargine to a glucagon-like peptide-1 agonist, dulaglutide. In terms of treatment for active lesions, one case report noted excellent response to topical timolol 0.5% ophthalmic solution when applied to the affected area three times per day for 6 weeks.[1] Since our patient had already tried topical corticosteroids and antibiotics, we elected to treat with topical timolol 0.5% ophthalmic solution. Some response was noted with application but not total clearance. This prompted the addition of oral propranolol 40mg twice daily, which has since been titrated to 60mg twice per day and is being tolerated well. The patient continues to see great improvement in the erythema, pain, and number of lesions, and has not developed any new ulcerations at other sites on the body.

Conclusion

We present a unique case of long-acting injectable insulin-induced RAE, a condition not previously reported in the literature. Although trauma-induced RAE has been documented, this case expands the understanding of potential triggers by identifying insulin injections as a novel cause. Given that current insulin packaging does not list this complication, it is important for dermatologists to recognize RAE as a possible side effect of injectable insulin. Furthermore, our patient's positive response to both topical and oral beta-blockers offers valuable insight into potential therapeutic options.

Potential conflicts of interest

The authors declare no conflicts of interest.

References

1. Bhatia R, Hazarika N, Chandrasekaran D, et al. Treatment of posttraumatic reactive angioendotheliomatosis with topical timolol maleate. *JAMA Dermatol*. 2021;157:1002-1004. doi:10.1001/jamadermatol.2021.1770. PMID:34106199

2. Faulkner C, Jabbour AJ, Kanik AB, et al. Reactive Angioendotheliomatosis following Ad26.COV2.S vaccination. *Cutis*. 2023;112(Dec):E20-E23. doi:10.12788/cutis.0920. PMID:38290076

3. McMenamin ME, Fletcher CD. Reactive angioendotheliomatosis: A study of 15 cases demonstrating a wide clinicopathologic spectrum. *The American Journal of Surgical Pathology*. 2002;26:685-697. doi:10.1097/00000478-200206000-00001. PMID:12023572

4. Kim D, Baraniuk J. Delayed-type hypersensitivity reaction to the meta-cresol component of insulin. *Ann Allergy Asthma Immunol*. 2007;99:194-195. doi:10.1016/S1081-1206(10)60645-X. PMID:17718109

5. Modi KD, Gadge PV, Jain P, et al. Clinical challenges with excipients in insulin formulations and role of concentrated insulin. *International Journal of Basic & Clinical Pharmacology*. 2019;8:821-826. doi:10.18203/2319-2003