

Allergic Contact Dermatitis to VenaSeal After Chronic Venous Insufficiency Treatment Mimics Phlebitis

To the Editor:

We report the case of a 42-year-old woman with erythematous-edematous reaction in the left leg 7 days after surgery for chronic venous insufficiency through venous occlusion with VenaSeal (Medtronic, Minneapolis, MN). The patient presented with pain and increased local temperature along the internal saphenous vein, without other associated manifestations. The emergency department diagnosis was acute phlebitis. Treatment with oral anti-inflammatory drugs (ibuprofen 600 mg every 8 hours) did not yield improvement after 3 weeks. The patient was referred to the dermatology department after discontinuation of treatment. Physical examination showed an erythematous trajectory along the internal saphenous vein of the left leg (Fig. 1A), associated with pain and induration on palpation. Skin ultrasound (Fig. 1B) showed hyperechoic intraluminal structures (corresponding to VenaSeal), associated with increased vascular Doppler and hyperechoic structures around the saphenous vein, compatible with inflammatory reaction. A possible hypersensitivity reaction to VenaSeal was suspected. Patch tests were performed with the extensive European series, acrylate series, cyanoacrylate series, and VenaSeal "as is." The patch test was read and interpreted according to the recommendations of the International Contact Dermatitis Research Group at 48 and 96 hours. The reading showed a positive reaction for VenaSeal (Fig. 1C) only. The patient was diagnosed with phlebitis-like allergic contact dermatitis caused by VenaSeal. No treatment was prescribed, and only the evolution of the allergic contact reaction was observed. Follow-up at 4 weeks showed complete improvement, with no evidence of erythema, pain, or any other local or systemic manifestation.

VenaSeal is a medical adhesive tissue that has revolutionized the treatment of chronic venous insufficiency. The main component is *n*-butyl-2-cyanoacrylate. In February 2015, the Food and Drug Administration approved the use of VenaSeal in the treatment of varicose veins.¹ The treatment is performed in an endovascular ultrasound-guided manner, and the intraluminal injection of VenaSeal is performed along the entire length of the internal saphenous vein. There are few publications in the literature on possible complications related to the use of VenaSeal. In the literature, there are reported cases with systemic symptoms (fever and general malaise)² and pictures of phlebitis-like

reaction.³ However, severe phlebitic reactions have not been reported. It is important to include this type reaction in the differential diagnosis, because it could be confused with cellulitis, and require an alternative treatment.

Why patients may develop an allergic reaction to VenaSeal is not known. Cyanoacrylates are histotoxic, leading to the generation of lipid peroxidases, which activate prostaglandin and thromboxane synthesis.⁴ Sensitization does not appear to be related to previous contact with other cyanoacrylates. In our contact eczema unit, a study was carried out with 20 controls in which, on suspicion of allergic contact eczema, VenaSeal was patched together with a series of acrylates and cyanoacrylates, without showing cosensitization to any of the allergens. Patch testing before the use of VenaSeal is not recommended. A hypersensitivity reaction to VenaSeal could be induced by persistence of intraluminal monomers if polymerization was incomplete, and in some areas the *n*-butyl-2-cyanoacrylate came into contact with the venous blood, a situation most likely perhaps in membranous folds of the venous valves. Pretreatment with nonsteroidal anti-inflammatory drugs and antihistamines for 10 days before the procedure⁵ has not been shown to prevent phlebitis-like inflammatory reaction.

Although the incidence appears to be very low, it is important to suspect an allergic reaction to VenaSeal when a patient has a phlebitis-like rash. Direct communication with the angiology department is essential to allow diagnostic confirmation and appropriate treatment.

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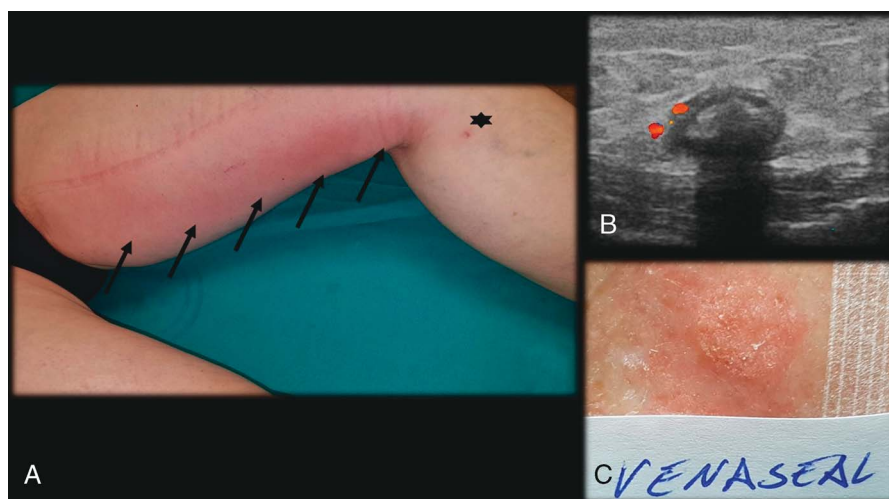


Figure 1. A, Blotchy erythematous eruption extending from the medial surface of the left leg. The arrows indicate the course and extent of the phlebitis-like reaction. The star shows the exit zone of the intraluminal process. B, Cutaneous ultrasound (Esaote 18 Hz) shows hyperechoic structures around the vein associated with intraluminal hyperechoic structures (VenaSeal). The acoustic shadow produced by VenaSeal is observed. C, Positive patch test reaction to VenaSeal at 96 hours.

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Treatment of Checkpoint Inhibitor–Induced Vitiligo in a Patient With Metastatic Renal Cell Cancer

To the Editor:

Although immune checkpoint inhibitors (ICIs) were originally used for metastatic melanoma, their efficacy has popularized their use in nonmelanoma malignancies. Immune checkpoint inhibitors include anti–cytotoxic T-lymphocyte–associated protein 4 (eg, ipilimumab, tremelimumab) and anti–programmed cell death protein 1/ligand 1 (eg, pembrolizumab, nivolumab, cemiplimab, durvalumab), drugs that reinstate the endogenous antitumor response by inhibiting negative regulators of immune activation such as cytotoxic T-lymphocyte–associated protein 4 and programmed cell death protein 1/ligand 1. This mechanism is thought to activate cytotoxic CD4⁺/CD8⁺ T cells and trigger immune-mediated toxicities against healthy tissues. Cutaneous adverse events are the most common ICI-induced toxicities across all tumor types (all-grade incidence of 24.28% with nivolumab, 50.56% with nivolumab-ipilimumab combination) with a median onset time of 2 months.^{1,2}

The ICI-induced vitiligo in melanoma patients is often untreated because of the fair-skinned predominance in melanoma patients and the risk for iatrogenic skin cancer with ultraviolet (UV) phototherapy. Literature on the longstanding stability of the depigmentation and its use as a prognostic marker for ICI-treated melanoma patients has further discouraged aggressive treatment.^{2,3} However, with the broadening indications for ICI use beyond melanoma, patient demographic includes more skin-of-color (SOC) patients reporting rapid depigmentation.⁴ Studies with SOC patients show that this supposedly asymptomatic disease can in fact provoke depression, isolation, and thoughts of harming oneself.⁵ This prompts the presumed irreversibility of ICI-induced vitiligo to be reconsidered.

We present the case of a 56-year-old Hispanic man with Fitzpatrick skin type III who developed vitiligo after ICI treatment for metastatic renal cell cancer. After a right nephrectomy in April 2018, the patient received nivolumab 240 mg and ipilimumab 90 mg every 3 weeks for 2 cycles. Patient transitioned to nivolumab 240 mg every 4 weeks until May 2019, at which point imaging showed complete remission of the renal cell carcinoma, and nivolumab use was suspended. Two months after cessation and 12 months after starting ICI therapy, the patient presented with depigmented macules coalescing into patches on hands, underarms, and abdomen. He denied previous personal or family autoimmune or cutaneous disease history.

To address the vitiligo, patient was prescribed topical triamcinolone 0.1% twice a day applied to the affected areas by the oncologist and switched to clobetasol 0.05% ointment once a day every other week by the dermatologist. Upon seeing no evidence of repigmentation after 5 months, he then started narrowband UVB phototherapy to affected areas three times every week for 6 weeks, with the instruction to continue applying clobetasol

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