Severe phlebitis-like abnormal reaction following great saphenous vein cyanoacrylate closure

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ABSTRACT

The VenaSeal closure system is a nonthermal, nontumescent technique that was approved by the U.S. Food and Drug Administration in 2015 for the treatment of superficial venous insufficiency. Studies have demonstrated a comparable efficacy and safety profile to thermal ablation procedures. We report a case of a middle-aged woman who developed a severe, prolonged phlebitis-like reaction requiring treatment with steroids and antihistamines after cyanoacrylate adhesive embolization. This adverse reaction is uncommon but usually self-limiting and is believed to be a type IV hypersensitivity reaction to the cyanoacrylate compound. Knowledge of this potential complication and its treatment are key, because the reaction may be severe with significant morbidity. (J Vasc Surg: Venous and Lym Dis 2019;7:578-82.)

Keywords: Venous insufficiency; Cyanoacrylate embolization; Phlebitis; Allergic reaction

Chronic venous insufficiency (CVI) is a common medical condition affecting between 10% to 35% of adults in the United States.[1] The etiology of CVI is multifactorial, but is most commonly due to dysfunctional valves in the superficial veins of the lower extremities with associated stasis and venous dilation.[2] This condition may be progressive and disabling, leading to symptoms and signs of heaviness, swelling, pain, itching, cramping, skin changes, and ulcerations.[1,2] Over the last few years, there have been major shifts in the treatment of CVI. Until 10 years ago, the gold standard for treatment of varicose veins was high ligation with stripping.[3] Endovenous thermal ablation (EVTA) techniques with laser or radiofrequency ablation (RFA) have been shown to have high venous closure rate as well as superior safety profiles.[3] Thus, EVTA have largely replaced more invasive surgical interventions.[1,4] One of the limitations of EVTA is the need for tumescent anesthesia to provide local anesthesia and protect surrounding tissues from thermal injury.[2]

In February 2015, the Food and Drug Administration approved the use of cyanoacrylate embolization (CAE) in the treatment of varicose veins.[1] CAE is a nonthermal, nontumescent technique that involves the introduction of cyanoacrylate adhesive in the vein leading to polymerization, inflammation, and occlusion of the vein.[1] This technique has gained interest because it causes no thermal injury and there is no need for multiple infusions of tumescent anesthesia.[4] Several studies have reported satisfactory safety and efficacy profile of CAE.[1,2,4-9] However, a common side effect with CAE is a self-limiting phlebitis-like abnormal reaction (PLAR) with a reported incidence as high as 25.4%.[10] There have been no case reports in the literature of severe phlebitic reaction to CAE. We report a case of a severe phlebitis-like allergic reaction after CAE of the great saphenous vein (GSV) in a middle-aged woman. Consent was obtained from the patient who was agreeable for publishing this case report.

CASE REPORT

A 65-year-old Hispanic woman with past medical history significant for hypertension, hyperlipidemia, obesity (body mass index of 32 kg/m^2), CVI, and varicose veins presented to the vascular surgery clinic with complaints of bilateral lower extremity heaviness, pain, and swelling. She had previously undergone RFA of the left GSV with stab phlebectomy of varicosities 4 years prior for a healed venous ulceration. Her symptoms are worse during the course of the day. She has no past medical history of deep venous thrombosis, heart failure, or liver or kidney disease. She denied any allergy to glue or adhesives. On physical examination, her vital signs were within normal limits. She had bilateral lower extremity pitting edema with class C3 venous disease on the right and C5 on the left. A lower extremity venous incompetence study revealed valvular reflux of the right GSV for 1006 milliseconds at the level of the saphenofemoral junction (SFJ) and the proximal thigh with a maximum vein diameter of 9.4 × 9.4 mm (Fig 1). The right GSV was subfascial in the thigh at 1 to 2 cm below skin level and then becomes suprafascial in the calf. There was also recanalization of the left GSV with partial chronic thrombosis and reflux for 2378 milliseconds with a maximum diameter of 6.2 × 5.9 mm. The short saphenous veins were competent bilaterally. The patient was compliant with compression therapy for several months and failed conservative management. Venous ablation was recommended for management of her symptoms. Intervention was

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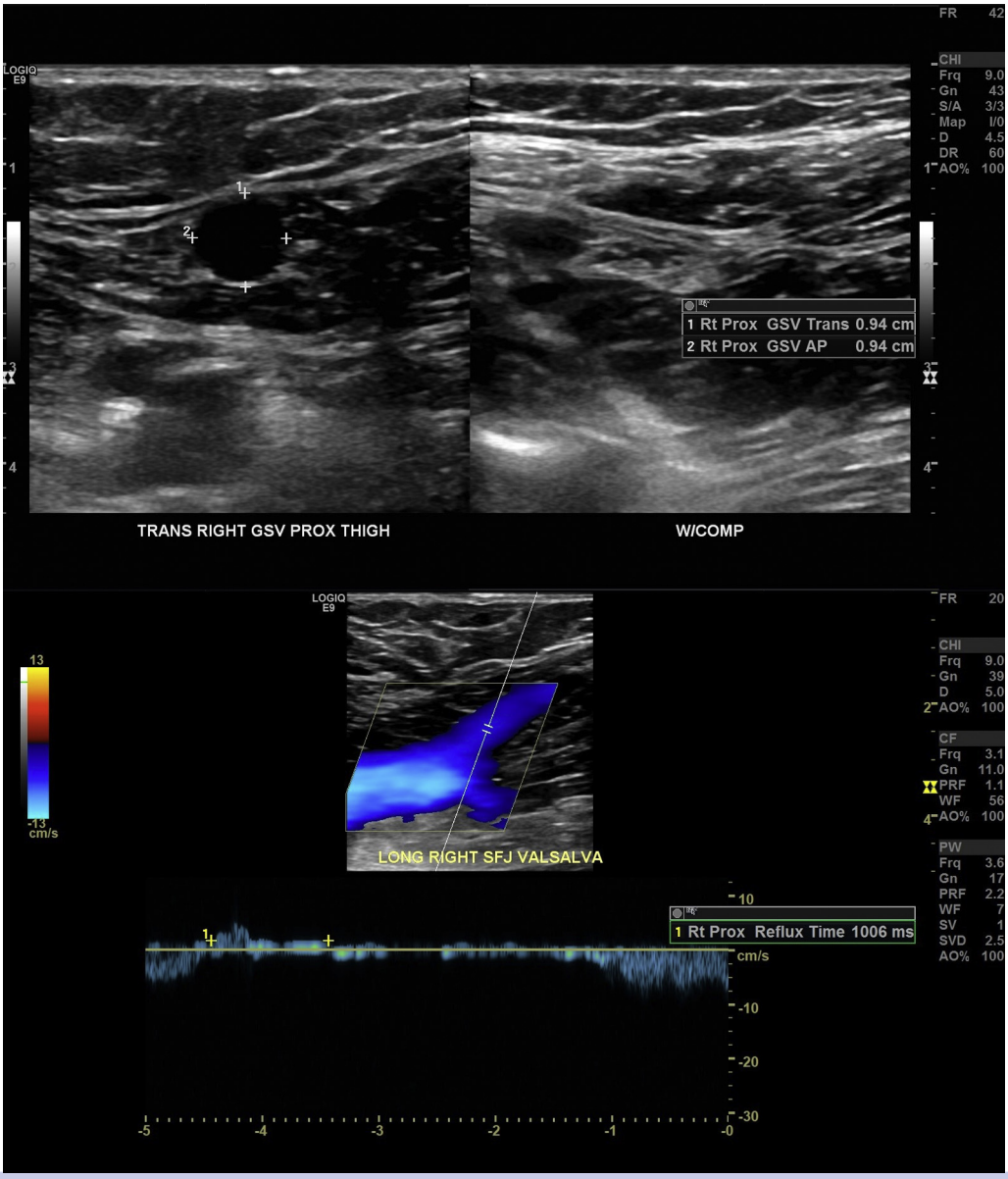

Fig 1. Preprocedure venous incompetence study showing the right great saphenous vein (*GSV*) measuring 9.4 × 9.4 cm with reflux of greater than 500 milliseconds.

planned on the right leg first because that side was more symptomatic for the patient.

The VenaSeal Closure System (Medtronic, Minneapolis, Minn) was used for closure of the right GSV. The cyanoacrylate adhesive was primed into the 5F delivery catheter and this catheter/syringe combination was attached to the dispenser gun. This was then introduced through the 7F sheath and positioned 5 cm caudal to the SFJ under ultrasound guidance. Two initial aliquots (0.2 mL) are injected proximally with 3 minutes of compression. Then, 1 aliquot (0.1 mL) is injected every 3 cm moving distally with 30 seconds of compression along the entire course of the GSV. After the last injection and compression sequence, the catheter and introducer sheath were pulled out of the site. The puncture site was closed with Steri-Strips. The total length of GSV treated was 50 cm using 1 mL of cyanoacrylate. Ultrasound examination confirmed closure of the treated GSV with no deep vein thrombosis at the SFJ. The patient did well immediately after her procedure and was discharged home.

On postoperative day (POD) 5, she was seen in the clinic, ambulating with no difficulty and had minimal pain at the site of venous ablation. An ultrasound examination done during this visit confirmed successful closure of the vein (Fig 2) with no evidence of deep vein thrombosis. However, on POD 6, she presented back to clinic with worsening pain, erythema, and itching at the medial thigh. On examination, she had mild erythema over the GSV. An ultrasound examination was repeated and was unchanged. She was diagnosed with phlebitis and was sent home on nonsteroidal anti-inflammatory drugs (NSAID) for symptomatic relief. A trial of compression therapy

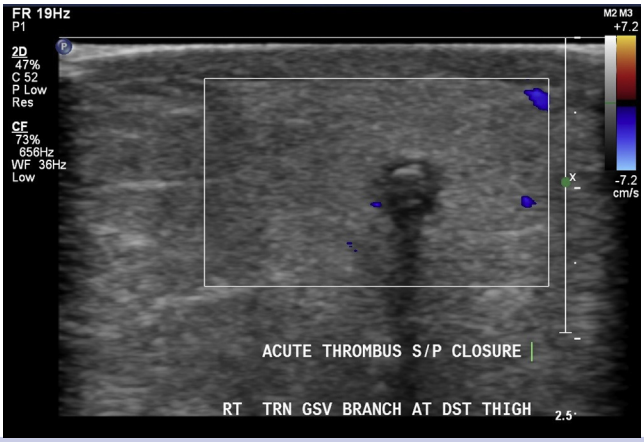

Fig 2. Postprocedure duplex ultrasound examination confirming closure of the right great saphenous vein (*GSV*).

was attempted for symptomatic relief, but the patient reported increasing pain with that modality. On POD 8, she came into the emergency department with severe worsening pain, erythema, itching, and swelling in her medial thigh (Fig 3, *A*). She was unable to ambulate because of her pain. She denied fever or chills. Her white blood cell count was 7500 cells/μL. She was

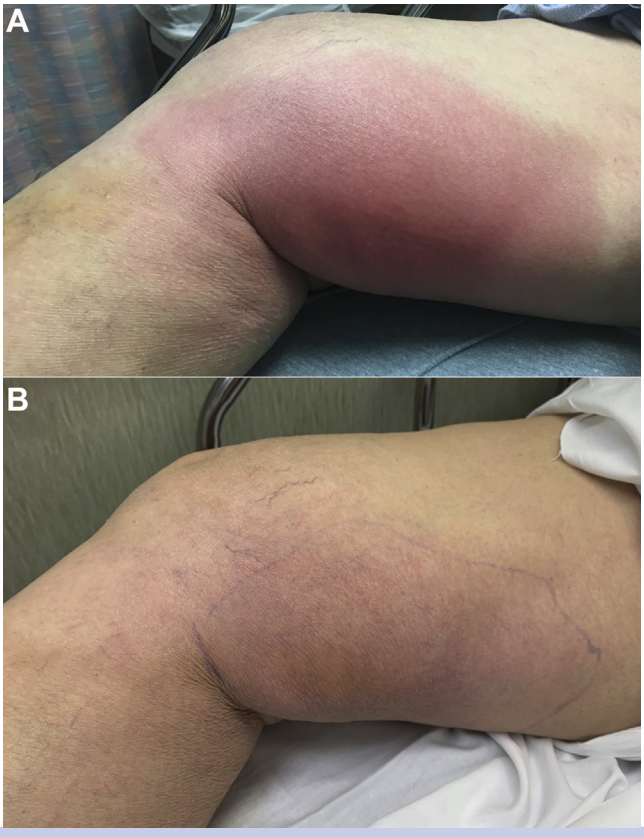

Fig 3. A, Right medial thigh erythema and swelling noted on postoperative day (POD) 8. **B,** Improvement of the erythema after steroid and antihistamine therapy during the clinic visit on POD 12.

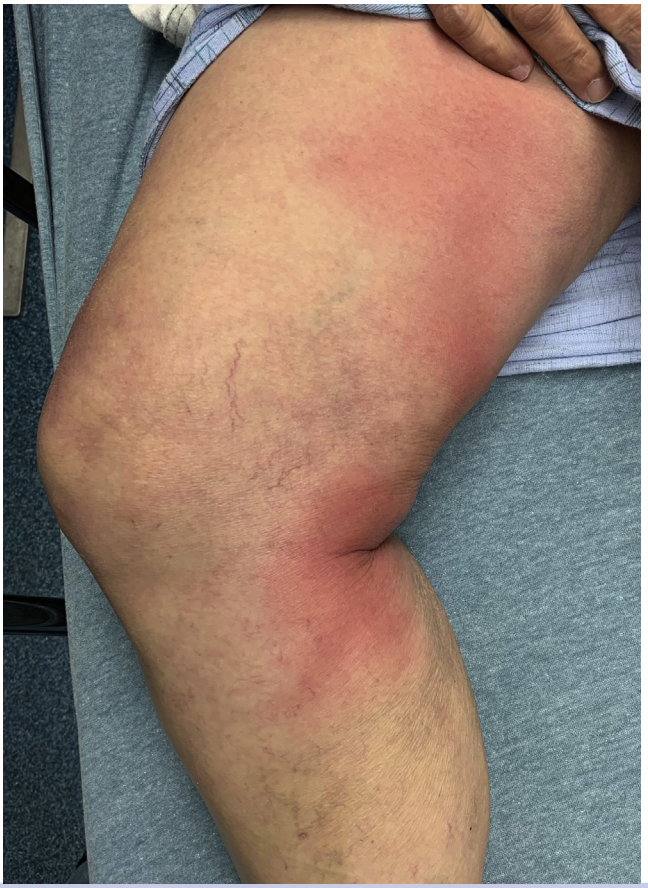

Fig 4. Relapse of the inflammatory signs at the site of the great saphenous vein (GSV) ablation at the medial thigh on postoperative day (POD) 18.

admitted to the hospital for concern of a severe phlebitis-like allergic reaction to the cyanoacrylate. She was started on methylprednisolone orally and diphenhydramine (Benadryl) and her symptoms improved. She was discharged home after 2 days to continue her steroid and antihistamine therapy for a total of 10 days. She was seen in clinic on POD 12 and was doing better. Her erythema and swelling had decreased markedly (Fig 3, *B*), although she continued to complain of pain and difficulty ambulating. On POD 18, she represented to the emergency department again with relapse of her symptoms (Fig 4). She had completed her prescribed therapy the day before this. She was restarted on her steroid therapy and was scheduled to follow up in clinic. On POD 20, she was seen in clinic with improvement of her symptoms (Fig 5). Steroids were discontinued after a few days and she was seen in clinic 1 month after her procedure with near resolution of her erythema and swelling.

DISCUSSION

Over the last few years, CAE has gained interest as a nonthermal, nontumescent technique for the treatment of CVI.[1] The most common side effect of CAE is PLAR, which is characterized by erythema, swelling, itching, pain, and tenderness over the treated vein.[5,8,10] The

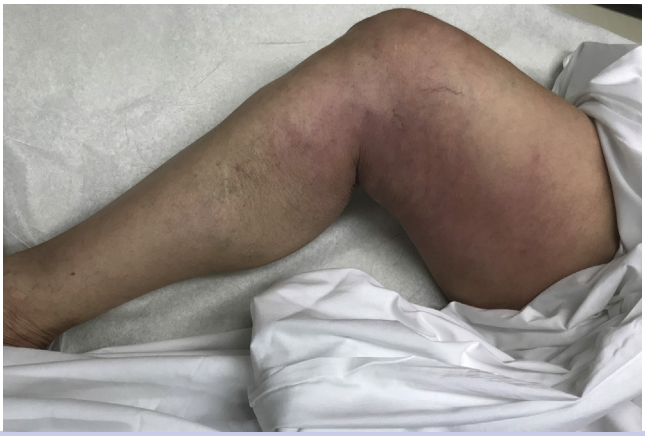

Fig 5. Improvement of right thigh erythema noted in the clinic visit on postoperative day (POD) 20.

incidence of PLAR is variable. Park et al[10] reported an incidence of 25.4% in an Asian population. This is higher than the incidence reported in the American (16%-20%) and European literature (11.4%).[2,6-8] In a randomized, controlled trial, Morrison et al[2] described that phlebitis was seen more commonly with CAE than with RFA, although finding this was not statistically significant. PLAR usually presents between 3 and 25 days after the procedure with an average time of 13.6 days.[10] Typically, it is mild and self-limiting lasting an average of 5.0 to 6.5 days.[6,7] The timing of presentation of our patient was consistent with the literature, but her reaction was persistent for more than 2 weeks and recurred after cessation of her steroids. PLAR occurs more commonly with GSV than small saphenous vein after CAE, and occurs more commonly with suprafascial GSV then subfascial GSV.[10] This may be due to the fact that suprafascial GSV are closer to the skin and, thus, more visible, allowing for more detection of this reaction.

The pathophysiology of PLAR is different from phlebitis associated with endothermal ablation.[8] Cyanoacrylate compounds have been associated with allergic contact dermatitis.[8,11] Studies have also shown cyanoacrylate to be histotoxic, leading to the generation of lipid peroxidases, which activate prostaglandin and thromboxane synthesis.[12] Because the mode of action of cyanoacrylate is causing an inflammatory reaction, which results in venous occlusion, PLAR could represent an exaggerated inflammatory reaction to the cyanoacrylate glue. Furthermore, Park et al[10] suggested that PLAR is due to a type IV hypersensitivity reaction to cyanoacrylate. This would explain why the reaction takes 1 to 2 weeks to develop, as well as the racial difference in the incidence of PLAR. In patients undergoing bilateral GSV CAE, bilateral PLAR was noted in 85.2% of cases, which may suggest that PLAR is a systemic rather than a localized reaction.[10] Our patient did not have a history of adhesives allergy. However, it is not uncommon for the patient to be unaware of her allergies or for a prior exposure to go unnoticed. For this reason, we would highly encourage testing for any allergy to cyanoacrylate glue before CAE. An allergic reaction detected should be a contraindication to performing this procedure.

The vast majority of PLAR associated with CAE are mild and transient, and managed with over-the-counter NSAIDs.[2,6] Because PLAR is thought to be due to an allergic reaction to cyanoacrylate, antihistamines and steroids have been used in its treatment. Park et al[10] described four prophylactic strategies for PLAR after the procedure which include NSAIDs for 5 days, NSAIDs for 14 days, NSAIDs and antihistamines for 10 days, and NSAIDs and antihistamines for 10 days, as well as a dose of intravenous dexamethasone. The incidence of PLAR was the same between all regimens, but the swelling and mean pain scores were decreased in the latter group.[10] These results question the role of prophylaxis in prevention of PLAR, but further randomized studies are required to evaluate that. It is worth mentioning that the role of NSAIDs and steroids may be nonspecific and solely function to improve the inflammation associated with PLAR. Given the severe, extensive, and symptomatic reaction experienced in our patient, we elected to treat her aggressively with a combination of NSAIDs, antihistamines, and steroids. The patient responded slowly to the treatment prescribed. After completing her 10-day course of steroids, the patient experienced a recurrence of her symptoms, which was likely due to premature termination of her medical therapy. She improved markedly with restarting her steroid therapy and, thus, we did not consider undertaking phlebectomy. The natural history of PLAR is generally benign; however, PLAR can be associated with increased pain scores after the procedure and an increased time to return to normal activities, as in our patient.[8]

CAE is a new technique that is becoming widely used in the treatment of CVI. It has well-established long-term safety and efficacy profiles when compared with RFA.[1] A major side effect is PLAR, which is usually self-limiting, although it can be severe, as in our patient. This finding stresses the fact that clinicians, namely vascular surgeons, need to be aware of this potential reaction because it may be a significant source of morbidity for patients. Despite its uncertain pathophysiology, PLAR seems to respond well to treatment with NSAIDs, antihistamines, and steroids. It is unclear if there is a role for these medications in the prophylaxis of PLAR.[10]

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