

Severe adverse reactions after cyanoacrylate endovenous ablation

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ABSTRACT

Hypersensitivity reactions after endovenous ablation with cyanoacrylate are relatively common, mild, and self-limited. However, rare cases of severe hypersensitivity reactions have occurred. To date and to the best of our knowledge, only two other cases requiring vein excision have been reported, and we present the third. Even rarer are cases with severe reactions featuring cyanoacrylate extravasation with skin perforation. In the present report, we describe the second case of skin perforation after successful cyanoacrylate endovenous glue embolization. The mechanism of these severe hypersensitivity reactions is unknown. Clinicians should consider this as a possible complication when using cyanoacrylate. Although rare, patients should also be advised of this adverse event when considering this alternative. (*J Vasc Surg Cases Innov Tech* 2023;9:101309.)

Keywords: Cyanoacrylate; Endovenous ablation; Hypersensitivity; Minimally invasive

Hypersensitivity reactions are potential complications after endovenous *N*-butyl-cyanoacrylate (CA) ablation. Although generally mild, rare cases have occurred of severe hypersensitivity reactions. In the present report, we describe two such cases. The patients provided written informed consent for the report of their case details and imaging studies.

CASE REPORT

First patient. A 63-year-old woman reported pain, urticaria, and edema 96 hours after great saphenous vein (GSV) ablation. Given the persistence and severity of her symptoms, she was prescribed steroids by her primary care provider 3 months after ablation. Her symptoms were only ameliorated mildly with 10 mg of oral methylprednisolone. Her right GSV CA ablation (VenaSeal Closure System; Medtronic) had been performed 9 months prior by a different provider. Her leg was treated for swelling. The GSV treated length was 54.5 cm with 20 mL of CA. She denied any history of allergies, specifically autoimmune disorders and adverse reactions to adhesives. We saw her 9 months after CA, and duplex ultrasound demonstrated successful GSV closure from the saphenofemoral junction (SFJ) to the above-the-knee region. However, chemically induced chronic-appearing partially occluding thrombus was seen from the SFJ protruding into the common femoral vein (CFV). The GSV was incompetent below

the knee. Anticoagulation therapy was considered, but she declined. The methylprednisone was tapered off; however, her symptoms recurred within 3 days after cessation. She had no skin changes while taking methylprednisone (Fig 1, A). Shortly after stopping the steroids, she developed debilitating calf pain and swelling, with hemosiderin-like discoloration and a medial calf wound (Fig 1, B). Thus, she started steroids again. The results from CA patch allergy testing were unavailable in a timely manner. She was, therefore, offered vein excision. The steroids were gradually discontinued 1 week before surgery, and endoscopic vein excision was uneventful. Thrombus was noted from the above-the-knee region into the SFJ and confinements of the CFV lumen. Duplex ultrasound demonstrated foreign body evidence in the GSV from the above-the-knee area into the SFJ, with partial CFV occlusion consistent with CA. Histopathologic analysis was performed (Fig 1, C).

At her 2-week follow-up visit, she reported significant symptom improvement, and her calf wound had begun to heal. A follow-up duplex ultrasound demonstrated a patent CFV with no residual CA and no deep vein thrombosis. Pathologic examination demonstrated intraluminal foreign body giant cells, including vacuoles, subendothelial histiocytes, and fibroblasts (Fig 2), compatible with a type 4 hypersensitivity reaction. At 3 months after vein excision, her leg was asymptomatic.

Second patient. A 73-year-old man presented with a 9-year history of a recurrent ulcer on the right medial malleolus (Fig 3, A). Duplex ultrasound findings were negative for deep vein thrombosis and demonstrated an incompetent GSV and a calf perforator vein. The perforator vein fed a refluxing varicosity beneath the wound. Reflux was also found in the CFV and proximal femoral vein. He denied any history of specific allergies, specifically denying autoimmune disorders and adverse reactions to adhesives.

He underwent GSV and perforator vein VenaSeal ablation (perforator vein ablation via CA is not included in the instructions for use). The GSV treated length was 68 cm, using 25 mL of CA. Two days later, duplex ultrasound demonstrated successful GSV and perforator vein ablation. No obvious intraoperative complications such as vessel perforation or CA extravasation were noted.

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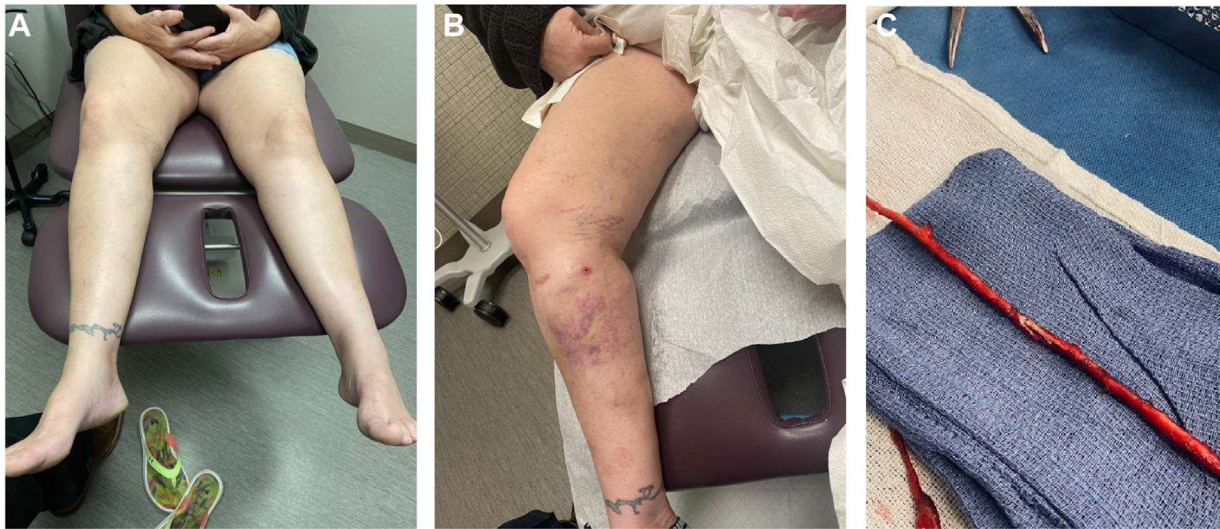


Fig 1. **A**, Photograph showing no skin changes after methylprednisone treatment. She had undergone Venaseal 9 months prior. **B**, Photograph showing a right medial calf wound with hemosiderin deposits that had developed 1 week after steroid cessation. **C**, Photograph showing excised right great saphenous vein (GSV) sent for histologic analysis.

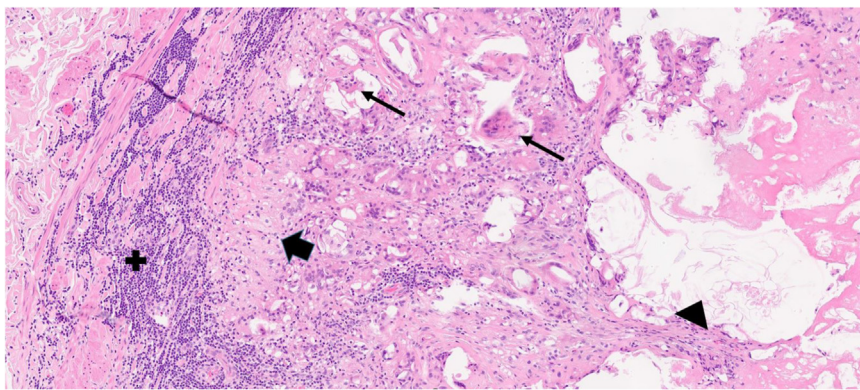


Fig 2. Photomicrograph of hematoxylin and eosin stain of right great saphenous vein (GSV) showing foreign body giant cells (*thin arrows*), histiocytes (*thick arrows*), and foci of lymphocytic inflammation (*plus sign*), with intraluminal foreign material (*arrowhead*) more visible at this magnification (high-power magnification, $\times 200$).

At 3 months of follow-up, his ulcer had healed (**Fig 3, B**). During that visit, he reported that 9 weeks after the index procedure, he had noted nontender erythematous subcutaneous lumps along the treated GSV. He had manually compressed these areas, resulting in skin eruption with foreign body excretion, later determined to be solidified CA fragments (**Fig 4, A**). On examination, he exhibited multiple superficial wounds along the GSV course and periwound erythema (**Fig 4, B**). He was given cephalexin, 500 mg, for 10 days, given the possible diagnosis of an infection. At 5 months of follow-up, his wounds along the GSV had healed. Nevertheless, he had gradually developed new similar wounds along the same GSV course. He reported further CA aggregate excretion via manual compression.

At 8 months, he had no new wounds, and his previous ones had continued to heal (**Fig 4, C**). His original ulcer remained

healed, and duplex ultrasound again demonstrated successful vein ablation.

DISCUSSION

The prevalence rates of hypersensitivity reaction after venous CA ablation range from 2% to 25% and are distinct from the traditional phlebitis occurring after endothermal ablation.¹⁻⁴ These hypersensitivity reactions generally manifest as a mild pruritic erythematous rash that typically resolves within 2 weeks.^{1,3,4} The onset of hypersensitivity reactions ranges from 1 to 23 days after a procedure.²⁻⁴ Types I and IV hypersensitivity reactions have been hypothesized.^{3,5,6} Chronic inflammation reactions have been observed histologically, and 1-year biopsies have depicted extravascular foreign body



Fig 3. A, Photograph showing chronic recurrence venous ulcer on right medial malleolus at initial visit. It had initially begun 9 years previously and had been open again for 6 months at presentation. **B,** Photograph showing healed venous ulcer malleolus at 3 months after right great saphenous vein (GSV) endovenous cyanoacrylate (CA) embolization via VenaSeal.

granulomas that enveloped multinucleated foreign body-type giant cells with glue extravasation.⁷

Our patients' CA hypersensitivity reaction are both suspect for a type IV hypersensitivity reaction. Our female patient had histopathologic findings of giant foreign body cells that further support a severe type IV hypersensitivity reaction. She had pruritus and discoloration, similar to other cases of CA hypersensitivity reactions. Our male patient had a severe atypical case. He was asymptomatic, other than skin erythema and foreign body excretion. Infection was considered in the differential diagnosis, although he did not have significant improvement with a broad-spectrum antibiotic. No other serum laboratory markers were obtained for either patient. We also carefully analyzed the ultrasound images for both patients, and no particular findings were identified for either case, pointing to the possibility of a hypersensitivity reaction after CA endovenous ablation.

The criterion for vein excision for the first patient was severe pain because conservative therapy had failed. We believe that surgery should be considered a last resort maneuver, a decision that must be individualized to each patient according to symptom severity. We found two other case reports of a severe CA hypersensitivity reaction after endovenous ablation that ultimately required vein excision. A 37-year-old woman developed whole body urticaria within 2 weeks postoperatively.^{1,2} She was treated with oral steroids twice, but her

hypersensitivity reaction recurred after steroid cessation. Also, a 49-year-old woman developed leg pain and erythema 13 days after CA ablation.⁵ She experienced improvement with oral steroids but later required vein excision. Patch testing was positive for CA. Immunohistochemical staining evidenced that most of the mononuclear cells involved were of the T4 subset and was suspect for a type IV hypersensitivity reaction.

To date and to the best of our knowledge, only one other case has been reported that involved skin perforation and foreign body discharge, similar to our patient. A 30-year-old man underwent GSV CA ablation and experienced painful inflammation along the treated vein 3 days postoperatively.⁸ He developed purple nodules along the treated GSV with subsequent skin rupture and CA extrusion. His symptoms resolved with oral steroids. Patch testing was positive for VenaSeal.

Severe adverse reactions involving CA vein ablation are extremely rare. At present, no clinically practiced standards capable of accurately detecting susceptibility for these reactions are available. Only patch testing can detect delayed-type hypersensitivity reactions, and kits are available but not on a commercial level,^{5,9,10} making it difficult to accurately screen such patients.

We no longer use CA for patients with a history of allergic reactions, especially reactions to adhesives, or if they have an autoimmune disorder. In addition, our consent process has been lengthened to include this as a possible complication.



Fig 4. **A**, Hard foreign bodies consistent with solidified fragments of *N*-butyl cyanoacrylate (CA) and other aggregate material. **B**, Photograph showing multiple small wounds due to skin breakdown and rupture with glue extrusion after CA extravasation at 3 months after right great saphenous vein (GSV) embolization with VenaSeal. **C**, Photograph showing wounds had healed significantly, although occasional weeping of serous fluid occurred. No new wounds had developed nor had any new glue fragments extruded at 8 months after the procedure.

CONCLUSIONS

CA hypersensitivity reactions are generally mild and self-limiting. However, severe hypersensitivity reactions have required vein excision. Rarer still are cases of granuloma formation, including foreign body extravasation with skin perforation. Greater efforts are required to generate susceptibility profiles and commercial testing methods to prevent hypersensitivity reactions in clinical settings. Clinicians should consider this possible complication and make patients aware of this risk before treatment.

REFERENCES

1. Gibson K, Ferris B. Cyanoacrylate closure of incompetent great, small and accessory saphenous veins without the use of post-procedure

2. Gibson K, Minjarez R, Rinehardt E, Ferris B. Frequency and severity of hypersensitivity reactions in patients after venaseal™ cyanoacrylate treatment of superficial venous insufficiency. *Phlebology* 2019;35:337-44.
3. Park I, Jeong MH, Park CJ, Park WI, Park DW, Joh JH. Clinical features and management of "phlebitis-like abnormal reaction" after cyanoacrylate closure for the treatment of incompetent saphenous veins. *Ann Vasc Surg* 2019;55:239-45.
4. Sermsathanasawadi N, Hanaroonsomboon P, Pruekprasert K, et al. Hypersensitivity reaction after cyanoacrylate closure of incompetent saphenous veins in patients with chronic venous disease: a retrospective study. *J Vasc Surg Venous Lymphat Disord* 2021;9:910-5.
5. Jones AD, Boyle EM, Woltjer R, Jundt JP, Williams AN. Persistent type IV hypersensitivity after cyanoacrylate closure of the great saphenous vein. *J Vasc Surg Case Innov Tech* 2019;5:372-4.
6. Parsi K, Roberts S, Kang M, et al. Cyanoacrylate closure for peripheral veins: consensus document of the Australasian College of Phlebology. *Phlebology* 2019;35:153-75.

7. Parsi K, Kang M, Yang A, Kossard S. Granuloma Formation following cyanoacrylate glue injection in peripheral veins and arteriovenous malformation. *Phlebology* 2019;35:115-23.
8. Lazzarini R, Duarte I, Ferreira AL. Patch tests. *An Bras Dermatol* 2013;88:879-88.
9. Muthupalaniappen L, Prick JA. Patch or blood test? A simple guide to allergy testing. *Malays Fam Physician* 2021;16:19-26.
10. Navarro-Triviño FJ, Cuenca-Manteca J, Ruiz-Villaverde R. Allergic contact dermatitis with systemic symptoms caused by venaseal. *Contact Derm* 2019;82:185-7.

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