OPEN

PRS GLOBAL OPEN

CASE REPORT
Technology

An Allergic Reaction in Contrast-enhanced Ultrasound Lymphography for Lymphovenous Bypass Surgery

Jess D. Rames, MD, MEng*
Nho V. Tran, MD*
Gina K. Hesley, MD†
Vahe Fahradyan, MD*
Christine U. Lee, MD, PhD†

Summary: Lymphedema following oncologic intervention can cause significant lifelong morbidity for patients in whom conservative management fails. The associated swelling, discomfort, pain, and recurrent cellulitis greatly diminish quality of life. Surgical procedures, including suction-assisted lipectomy, lymphovenous anastomosis (LVA), and vascularized lymph node transfers, show effectiveness in both volume reduction in affected extremities and symptom relief. However, the success of procedures like LVA is dependent on effective preoperative lymphatic mapping to identify suitable vessels for anastomosis. Traditional superficial lymphatic mapping uses near infrared fluorescence indocyanine green (ICG) imaging. Moreover, recent advances in contrast-enhanced ultrasound (CEUS) lymphography increased lymphovenous bypass target identification for LVA in the extremities.[7] CEUS lymphography uses microbubbles as a contrast-enhancing agent injected intradermally into the affected extremity with subsequent identification of superficial collecting lymphatic vessels using ultrasound. Although a recent report noted an uptick in severe and critical adverse drug reactions to an ultrasound contrast agent injected intravenously in stress echocardiography, adverse drug reactions associated with ultrasound contrast-enhancing agents in body ultrasound are rare. The safety profile and potential complications from CEUS lymphography in the lymphedema population have yet to be fully characterized. In this case report, the authors present the first cutaneous adverse drug event following a secondary exposure to the contrast used for CEUS imaging. Mechanisms and justifications for an immune-mediated process are explored, and a review of similar manifestations in other related contrast applications is discussed. *(Plast Reconstr Surg Glob Open 2024; 12:e5908; doi: 10.1097/GOX.0000000000005908; Published online 17 June 2024.)*

A 32-year-old female patient first presented to the lymphedema clinic with stage II (International Society of Lymphology) bilateral upper extremity edema that worsened over 5 years. Her oncologic history included Hodgkin lymphoma treated with a left neck lymphadenectomy and chemoradiotherapy 13 years prior. Her clinical course was complicated by right- and left-sided recurrence 2 and 6 years later, respectively; for this, she received a contralateral neck lymphadenectomy, repeated radiotherapy bilaterally, and an autologous stem cell transplant. Five years later, she was diagnosed with right breast lobular carcinoma in situ, prompting ipsilateral axillary lymph node dissection, bilateral nipple-sparing mastectomies, and bilateral immediate reconstruction with pedicled latissimus dorsi flaps over implants.

The patient first experienced symptoms of left upper extremity lymphedema approximately 12 years after her index surgery for Hodgkin's lymphoma. She would go on to develop contralateral lymphedema 5 years later. Conservative therapies, including daily compression therapy and elevation, were attempted with minimal success. Her physical examination was notable for bilateral non-pitting edema of the hands and forearms, with evidence of woody, indurated changes of the left upper extremity. Initial forearm circumferences were measured at 23 cm bilaterally; her upper arm circumferences were 30.5 cm on the left and 29.5 cm on the right.

Given the patient's clinical presentation and recalcitrant disease, bilateral lymphovenous anastomosis

*From the *Division of Plastic and Reconstructive Surgery, Mayo Clinic, Rochester, Minn; and †Department of Radiology, Mayo Clinic, Rochester, Minn.*

Received for publication February 5, 2024; accepted April 26, 2024.

DOI: 10.1097/GOX.0000000000005908

Disclosure statements are at the end of this article, following the correspondence information.

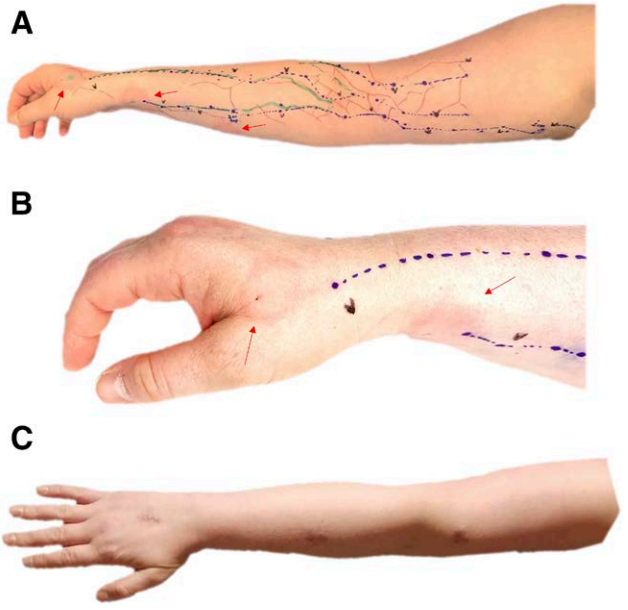

Fig. 1. Cutaneous reaction to Lumason intradermal injections for CEUS lymphography. Evidence of multiple wheals after lymphatic mapping are evident on the right (A) forearm (red arrows) and the (B) hand (red arrows) after contrast exposure during the second lymphovenous bypass/anastomosis procedure. The first procedure took place 2 months earlier on the contralateral arm without any reactions. C, Three weeks postoperative picture with resolution of wheals and improvement in lymphedema.

(LVA) surgery was pursued in a staged fashion. She developed interval cellulitis on her left hand, prompting earlier surgical intervention of her left upper extremity. Intraoperative contrast-enhanced ultrasound (CEUS) (Lumason, Bracco, Monroe Township, N.J.) and ICG lymphography were performed before LVA surgery. Based on the imaging results, two lymphovenous anastomoses over the dorsum of the hand and proximal forearm were performed. The patient was discharged the same day with no immediate postoperative complications noted.

Two months later, the patient underwent contralateral LVA surgery using the same intraoperative dual-imaging mapping protocol as before. Soon after the injection of the Lumason microbubble contrast for CEUS, the patient developed erythematous wheals localized to the injection sites (Fig. 1A and B). Intravenous Benadryl and methylprednisolone were administered. She remained clinically stable, and the procedure continued unabated. ICG lymphography was performed at different sites compared with Lumason injections. Two bypasses were performed over the dorsum of the hand, and one was performed at the proximal forearm. Because of the appropriate treatment of the allergic reaction, the LVA patency was not affected. Although the new rash persisted, she had no other clinical concerns at discharge.

At the patient's 3-month follow-up after her last procedure, she was healing well with no further cellulitis and lymphedema reduction in both upper extremities. During her most recent follow-up, the patient had achieved a total right upper extremity volume reduction of 11.36% from a baseline of 2493 cm^3 while continuing pneumatic compression therapy only at night. The right-sided skin wheals that she developed after contrast injection were completely resolved (Fig. 1C).

DISCUSSION

As new lymphatic mapping techniques emerge for LVA planning, it is important to be aware of potential adverse events. At our institution, patients anticipating LVA surgery undergo lymphatic mapping with traditional ICG imaging and optional CEUS. Our CEUS lymphography protocol uses Lumason sulfur hexafluoride lipid-type A microspheres as a contrast agent. This helps surgeons identify more potential sites for LVA.[1] Evaluating the efficacy of CEUS lymphography remains experimental; as such, the incidence of adverse drug reactions (ADRs) in this population is not well defined.

Of the 51 patients involved in our practice using CEUS for extremity lymphedema, this was the first patient to demonstrate site-specific welting consistent with a localized allergic reaction. We considered other possible etiologies, including sensitization to Duriprep or induced trauma. The first was deemed unlikely, given the localized nature of the reaction. Contrast injection was performed in the same fashion as during her previous surgery, ruling out trauma as a likely cause. The patient had no other contributory allergy history that warranted concern. Additionally, ICG lymphography performed immediately after CEUS lymphography did not result in the same reaction. In our patient, the cutaneous manifestation after her secondary contrast administration was consistent with a type 1 hypersensitivity reaction, given its immediate manifestation. In this reaction, IgE specific to a preexposed antigen triggers an immediate cutaneous eruption characterized by exposure-specific tissue swelling and erythema. In contrast, cell-mediated hypersensitivity reactions are often delayed.[2]

We performed a literature review to help approximate the expected frequency of such events, as CEUS becomes more widely adopted in plastic surgery. The 2023 American College of Radiology Manual on Contrast Media cites 29 (0.13%) adverse events in 23,188 patients who received SonoVue (Lumason).[3] In another study, isolated reactions at the injection site occurred in eight (0.02%) cases out of 34,478 CEUS examinations performed during a 6-year period.[4] For applications in stress echocardiography, intravenous injections of Lumason were associated with much higher ADR rates compared with Definity (Lantheus, N. Billerica, Mass.), another available ultrasound contrast agent. This included both mild ADRs (urticaria, itching, skin erythema, and gastrointestinal distress) and severe ADRs with systemic involvement (new onset throat tightness, stridor, wheezing, hypotension, and chest pain).[5] Table 1 compares the different ultrasound contrast agents available. ADRs have also been associated with prior administration of the pegylated coronavirus disease 2019 Moderna vaccine,[5] which our patient received in 2021. This association

Table 1. Comparison of Available Ultrasound Contrast Agents

Name	FDA-approved	Gas	Outer Shell	Range of Mean Bubble Size (μm)	Contains Polyethylene Glycol
Lumason (Sonovue)	Yes	SF_6	Lipid-type A	1.5–2.5	Yes
Definity	Yes	C_3F_8	Perflutren lipid microsphere	1.1–3.3	Yes
Definity RT	Yes	C_3F_8	Perflutren lipid microsphere	1.1–3.3	No
Optison	Yes	C_3F_8	Protein-type A	3.0–4.5	No
Sonazoid	No	C_4F_{10}	Phospholipid monolayer	2.0–3.06	No

All available ranges were determined from the individual supplies datasheets/websites or from publicly available documentation through the FDA.

points to polyethelene glycol as a possible immune trigger or potentiator of Lumason. Our application was intradermal and not intravenous, and the volume administered was significantly lower. This could have invariably affected the immunologic response to the contrast agent. We cannot definitely attribute the ADR to the contrast agent or the microbubble preparation itself. Regardless of the specific cause, plastic surgeons should be cognizant of the associated risks of this imaging modality.

Although the ADR in this case report was milder compared with others reported in the literature,[5,6] it underscores the need for attentiveness when using any contrast agent. Performing CEUS lymphography intraoperatively before LVA ensures a safe setting for managing ADRs. However, with the appropriate vigilance and response plans in place, outpatient CEUS lymphography is also feasible. Careful consideration of potential ADRs will be crucial, as these innovative lymphatic mapping techniques become more widely available.

CONCLUSIONS

CEUS lymphography, which involves injecting microbubble-based contrast agents intradermally, can cause ADRs. This case report is the first to document a cutaneous reaction following secondary exposure. It is important to evaluate advanced imaging techniques for lymphedema surgery, considering both their potential clinical benefits and safety concerns.

Jess D. Rames, MD, MEng
Mayo Clinic
Department of Plastic and Reconstructive Surgery
Rochester, MN 55905
E-mail: rames.jess@mayo.edu

DISCLOSURE

The authors have no financial interest to declare in relation to the content of this article.

REFERENCES

1. Jang S, Lee CU, Hesley GK, et al. Lymphatic mapping using US microbubbles before lymphaticovenous anastomosis surgery for lymphedema. *Radiology*. 2022;304:218–224.
2. Ardern-Jones MR, Friedmann PS. Skin manifestations of drug allergy. *Br J Clin Pharmacol*. 2011;71:672–683.
3. Piscaglia F, Bolondi L; Italian Society for Ultrasound in M, Biology Study Group on Ultrasound Contrast A. The safety of Sonovue in abdominal applications: retrospective analysis of 23188 investigations. *Ultrasound Med Biol*. 2006;32:1369–1375.
4. Hu C, Feng Y, Huang P, et al. Adverse reactions after the use of SonoVue contrast agent: characteristics and nursing care experience. *Medicine (Baltimore)*. 2019;98:e17745.
5. Ali MT, Johnson M, Irwin T, et al. Incidence of severe adverse drug reactions to ultrasound enhancement agents in a contemporary echocardiography practice. *J Am Soc Echocardiogr*. 2023;37:276–284.e3.
6. Arnouk S, Huynh Q, Saric M, et al. A case report of cardiac arrest after intravenous administration of sulfur hexafluoride (Lumason) ultrasound enhancing agent. *J Pharm Pract*. 2023;37:509–512.