OBSERVATION

Efficacy and Safety of Microfoam Sclerotherapy in a Patient With Klippel-Trenaunay Syndrome and a Patent Foramen Ovale

Pedro Redondo, MD, PhD; Gorka Bastarrika, MD, PhD; Alejandro Sierra, MD, PhD; Antonio Martínez-Cuesta, MD, MSc, FRCR; Juan Cabrera, MD, PhD

Background: Sclerotherapy with polidocanol microfoam injection under duplex guidance is a new treatment for venous malformations associated with Klippel-Trenaunay syndrome. Multidetector-row computed tomography (MDCT) venography is extremely helpful in the assessment of disease extension and the planning of therapy.

Observation: In this particular case, MDCT venography demonstrated the origin, course, and relationship to adjacent anatomical structures of aberrant vessels that configure the superficial venous system with an anatomically normal and patent deep venous system. At the end of the treatment, which consisted of 8 sessions of microfoam sclerotherapy within 12 months, a considerable reduction in the number and size of the percutaneously treated aberrant veins was observed. The obvious clinical improvement was objectively demonstrated with MDCT venography, which showed clear reduction in the number and size of treated veins. Further clinical investigation performed because of isolated migraine episodes related to the sclerotherapy session revealed that the patient had a patent foramen ovale. A transcranial Doppler examination during the procedure showed middle cerebral artery bubbles, which indicated right-to-left shunt. No cerebral damage was observed in a subsequent diffusion-weighted magnetic resonance examination.

Conclusions: Microfoam sclerotherapy is an effective treatment option in patients with Klippel-Trenaunay syndrome. MDCT venography allows diagnosis of the disease, planning of therapy, and assessment of response to treatment. Although foam-induced microembolism is a common phenomenon during sclerotherapy, in this report we demonstrate that polidocanol microfoam prepared with a low-nitrogen gas mixture is safe in a patient with a patent foramen ovale.

Arch Dermatol. 2009;145(10):1147-1151

Klippel-Trenaunay syndrome (KTS)[1] is a rare congenital anomaly defined by a triad of signs that consists of vascular stain, soft tissue and/or bony hypertrophy, and venous varicosities. Among available imaging strategies, multidetector-row computed tomography (MDCT) venography has been shown to enable overall evaluation of patients with this syndrome, not only for diagnostic purposes but also to plan adequate therapy.[2] In this sense, sclerotherapy with polidocanol microfoam injection under duplex guidance is considered the treatment of choice for venous malformations associated with KTS.[3-6] However, recent controversies with regard to the safety of sclerotherapy by means of microfoam, particularly in patients with a patent foramen ovale, have invigorated concerns about the broadening of possible applications of this minimally invasive treatment option. This contribution reflects for the first time, to our knowledge, objective clinical and morphologic evidence (by means of MDCT) of the safety and effectiveness of sclerotherapy by means of microfoam in a patient with a patent foramen ovale treated with a significantly larger amount of polidocanol microfoam than otherwise required to treat conventional varicose veins.

Author Affiliations: Unit of Vascular Malformations, Department of Dermatology (Drs Redondo, Sierra, and Cabrera), and Department of Radiology (Drs Bastarrika and Martínez-Cuesta), University Clinic of Navarra, School of Medicine, University of Navarra, Pamplona, Spain.

REPORT OF A CASE

A 25-year-old woman was admitted to our hospital with signs suggestive of KTS manifest as widespread venous varicosities and a segmental port wine stain, both of which affected her left leg. She reported intralesional pain. After giving written informed consent, she underwent direct MDCT venography with injection of a diluted (1:6) contrast agent via a peripheral lower-extremity vein to evaluate the

©2009 American Medical Association. All rights reserved.
Downloaded From: http://jamanetwork.com/ on 06/20/2013

Figure. Clinical and multidetector-row computed tomography venography images from a 25-year-old woman with Klippel-Trenaunay syndrome. Upper row, Initial images; lower row, follow-up images. A and D, Anterior views (left); B and E, Lateral views; and C and F, Posterior views. At admission she presented with abundant phlebectasias in her right lower extremities. The follow-up examination performed 12 months after 8 sessions of polidocanol microfoam sclerotherapy demonstrated disappearance of most of the abnormal venous vessels.

origin and extent of venous malformations and assess patency of the deep venous system (DVS) before therapy. The examination revealed that aberrant vessels originated from the superficial venous system, whereas the DVS appeared morphologically healthy and patent. There was an absence of intramuscular venous malformations. By means of ultrasonography, we demonstrated the presence of venous reflux in the superficial venous system. On the basis of her clinical symptoms and MDCT findings, treatment with percutaneous polidocanol microfoam sclerotherapy was initiated.

This procedure was performed without administration of anesthesia to the patient. The method of preparation of polidocanol microfoam itself is based on the procedure described in granted European and US patents EP 656 203 and US 5 676 962, respectively.[7,8] At each session, 20 to 80 mL of polidocanol microfoam at concentrations of 0.25% to 2% (which corresponds to a moderate dose of 3-6 mL of the original liquid solution) was directly injected in marginal, great saphenous, and peripheral small veins via 20G and 23-25G needles, respectively. The injection was performed via ultrasonographic guidance. This approach allowed correct location of the needle at the insertion site and visualization of the initial effects of microfoam injection, such as spread of the sclerosing agent, displacement of blood, and vasospasm, detection of the arrival of the injected microfoam to the saphenous-femoral confluence, and avoidance of the entrance of the sclerosing solution into the DVS by compression of the site. To further protect the DVS from drainage of microfoam, the sclerosing solution was injected by means of 2 additional "closed-door" procedures (ie, with the affected limb raised [safety angle] and the foot dorsally flexed by sustained contraction of the medial gastrocnemius muscle). Limb elevation creates a gradient whereby the DVS has a higher blood pressure, whereas foot dorsal flexion blocks the intramuscular veins by calf muscle contraction. Even with these maneuvers, the passage of small quantities of foam into the DVS cannot be totally prevented. Once injected, compression was applied to avoid dislocation of the microfoam column. The patient remained in the supine position for 15 to 20 minutes. Percutaneous treatment was complemented by the placement of a compression stocking on the patient (Struva 23-mm Hg stocking; Medi-Bayreuth, Bayreuth, Germany), which is worn for 7 to 15 days after injection. The first session was accomplished with significant symptom relief. The patient was

©2009 American Medical Association. All rights reserved.
Downloaded From: http://jamanetwork.com/ on 06/20/2013

subsequently treated for 12 months with 8 microfoam sclerotherapy sessions.

Interestingly, shortly after the sclerotherapy session the patient experienced an isolated migraine episode that lasted for 10 minutes without any associated neurologic deficit. After further investigation the diagnosis of patent foramen ovale was made. In fact, a transcranial Doppler examination performed during the second sclerotherapy procedure revealed bubbles in the middle cerebral artery, a finding consistent with right-to-left shunt. As a consequence, the patient underwent extensive clinical and imaging monitoring, with the inclusion of diffusion-weighted magnetic resonance imaging at 24 hours, which showed no evidence of cerebral damage.

Six months after the final sclerotherapy session, the patient was reevaluated with further iconography and indirect MDCT venography. At this point, examinations revealed significant clinical improvement and considerable reduction in the number and size of the percutaneously treated aberrant veins (**Figure**).

COMMENT

Venous malformation is the main cause of morbidity in patients with KTS. In current clinical practice a constellation of diagnostic techniques, with the inclusion of color Doppler ultrasonography, computed tomography, magnetic resonance imaging, and intravenous digital subtraction angiography, is available to image vascular structures. Limited ability to display the full extent of large lesions and operator dependence are major drawbacks of ultrasonography.[9] Being considered the standard of reference for the evaluation of vascular structures and the accurate separation of high-flow and low-flow vascular malformations,[10] digital subtraction angiography remains, however, invasive and, thus, may not be the most appropriate tool for the initial evaluation of patients without overt clinical signs of arteriovenous shunting. Magnetic resonance imaging is an emerging technique that has repeatedly shown its ability to noninvasively evaluate vascular structures, but its cost is too high and its availability too low. Recently, although it is of limited value to assess venous hemodynamics, MDCT has been proven to be an excellent diagnostic tool for the assessment of individuals with KTS; the evaluation of the characteristic morphologic features that compound KTS; the depiction of the anatomical origin, course, and relationships of varicose veins and venous malformations; and help with therapy decision making.[2]

Chronic venous insufficiency is the most frequent cause of pain in patients with KTS.[11] In these patients, the classic surgical approach of staged ligation can serve as a palliative treatment. Aggressive excision of venous malformations often involves excessive bleeding and loss of function, and debulking leads to further lymphedema and nonhealing wounds.[12] The association between extensive venous malformations and hypercoagulability is well established.[13] The magnitude of the coagulopathy correlated with the severity of the malformation. Patients with KTS are at higher risk for thrombosis and recurrent pulmonary embolism than are those with less extensive, isolated venous malformations. This potential complication increases in some situations, such as surgery and prolonged immobility.[14] Thus, a less invasive and more effective approach may be desirable for the treatment of patients with complex venous malformations.

Conventional sclerotherapy with liquid sclerosants, which is a palliative treatment in most vascular anomaly cases, offers good outcomes in patients with small malformations. This technique is indicated as preoperative support to reduce the size of the lesion before surgery or as a postoperative complement.[15] In contrast, in the clinical scenario of large vascular malformations, conventional sclerotherapy has been demonstrated to be ineffective. Sclerotherapy with ethanol, the most widely used agent in the treatment of this type of lesions, is highly aggressive and associated with major complications attributable to lack of control over the injected liquid. Moreover, treatment with ethanol is not readily repeatable, and repeatability is essential for sclerotherapy because partial recanalization after the intravascular thrombosis is frequent.[16]

Foam sclerotherapy is more effective than liquid sclerotherapy in the treatment of symptomatic venous malformations.[17] Sclerosing foam is generally defined as a mixture of gas and liquid sclerosing solution (detergent type) with tension-active properties.[18] The foam physically displaces the blood contained in the vessels, which facilitates a more homogeneous distribution of sclerosant on the endothelial surface and prolongs sclerosant-endothelium contact time. Therefore, microfoam enables the intravascular administration of a more precise dose of sclerosant.[19,20]

Foam can be produced with a variety of agitation techniques that result in differences in bubble size and rate of reabsorption.[21] Sclerosant microfoam offers the best results when it is made with carbon dioxide. This physiologic gas is nontoxic and highly soluble; thus, large amounts can potentially be administered. When carbon dioxide is mixed into the surfactant liquid sclerosant, microbubbles of reduced diameter of sufficient stability can easily be obtained.[22,23]

Large case series demonstrate the efficacy and safety of the treatment of varicose veins with foam sclerotherapy.[24,25] The incidence of adverse events is low and may be related to the method of foam production. In a recent study, Frullini and Cavezzi[26] documented only 7 events among the 453 treated patients. We observed scotoma with or without migraine (which, in each instance, mimics the previous migraine aura of the patient) in 1% of cases without any other associated neurologic deficit. Recent literature reflects that the occurrence of distal embolism most likely relies on the size of bubbles and the solubility of the gas used.[27] On the basis of this assumption, BTG International, Ltd, is developing polidocanol-based sclerosant microfoam technology (Varisolve) into a pharmaceutical product. In an experimental in vivo model that uses the cremaster muscle of the rat, it has been shown that 2 types of the patented polidocanol microfoam (one of which is Varisolve; Provensis, Inc, West Conshohocken, Pennsylvania) perfuse through the arteriolar system without the circulation being affected, whereas another sclerosing microfoam obtained by means of the double syringe method with room

©2009 American Medical Association. All rights reserved.
Downloaded From: http://jamanetwork.com/ on 06/20/2013

air occludes the arteriolar system and holds up the circulation, which produces massive gas embolisms.[21]

Several authors applied the double syringe technique, which led to larger bubbles than our technique of dispensement of foam, which produces a highly controlled bubble-size distribution. In these homemade foams, the volume of gas that can be injected is limited by the low solubility of nitrogen, and only the concentration can be modified. A recent European consensus statement recommended 6 to 8 mL per session, but different published reports have used 3 mL up to 30 mL.[28] For polidocanol microfoam preparation, we used a very low nitrogen gas mixture, whereas other investigators used room air, which is associated with increases in bubble number and size.[29] In large vascular malformations, our group has used up to 100 mL of sclerosing microfoam without respiratory or neurologic complications. The ability to use such large volumes may rely on the use of carbon dioxide instead of room air.[30]

A major concern of percutaneous injection of polidocanol microfoam is the presence of bubbles in cardiac cavities. In cases of patent foramen ovale or other anatomical entities that cause right-to-left shunt, sclerosing bubbles may pass from the venous system to arterial circulation. This fact should not be ignored because the prevalence of patent foramen ovale is approximately 26% in the general population,[31] and foam-induced bubbles in the cerebral circulation are not an uncommon phenomenon during percutaneous foam sclerotherapy.[32] Although there is an ongoing debate with regard to the possibility of neurologic complications associated with the use of foam, even in the presence of a patent foramen ovale the flow from right to left appears only during increased pressure in the right side, such as during the Valsalva manuever.[33,34] A recent report[35] describes a case of a paradoxical cerebral air embolism caused by a patent foramen ovale. In the patient discussed in this report, clear evidence of right-to-left shunt via a patent foramen ovale was demonstrated. A transcranial Doppler examination performed during the procedure demonstrated the presence of bubbles in the middle cerebral artery, which indicates right-to-left shunt. However, shunting of the sclerosing agent did not cause brain damage detectable by diffusion-weighted magnetic resonance imaging.[36]

In conclusion, microfoam sclerotherapy is a promising treatment for venous malformations associated with KTS. This simple procedure is capable of causing the elimination or reduction of clinical symptoms from the first session onward, is easy to repeat should recurrences occur, and, because it is minimally iatrogenic, does not involve the risk of adverse effects. In these patients MDCT venography could be a highly sensitive technique of great help to map venous anatomy during preinterventional planning and to assess the response to treatment. Finally, in concordance with the results of ongoing studies,[37] we described a patient with a patent foramen ovale treated safely with larger volumes of polidocanol microfoam sclerotherapy than those otherwise required for varicose vein treatment.

Accepted for Publication: February 13, 2009.
Correspondence: Pedro Redondo, MD, PhD, Department of Dermatology, University Clinic of Navarra, 31008 Pamplona, Spain (predondo@unav.es).

Author Contributions: Dr Redondo had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Redondo and Bastarrika. *Acquisition of data:* Sierra, Bastarrika, Martínez-Cuesta, and Cabrera. *Analysis and interpretation of data*: Redondo and Martínez-Cuesta. *Drafting of the manuscript*: Redondo and Bastarrika. *Critical revision of the manuscript for important intellectual content:* Redondo, Bastarrika, and Cabrera. *Obtained funding:* Redondo. *Administrative, technical, or material support:* Redondo, Sierra, and Cabrera. *Study supervision:* Redondo, Bastarrika, and Sierra.
Financial Disclosures: The authors have no relevant financial interest in this article. The microfoam presented in the study was the subject of a patent application by Dr Juan Cabrera in 1993, and he has subsequently assigned the patents to BTG International Ltd, London, England. Provensis Ltd, London, a subsidiary of BTG International Ltd, has developed the patented microfoam concept into a pharmaceutical product, Varisolve, which is undergoing clinical trials in Europe and the United States.
Role of the Sponsor: The sponsors had no role in the design and conduct of the study; in the collection, analysis, and interpretation of data; or in the preparation of the manuscript, review, or approval of the manuscript.

REFERENCES

1. Klippel M, Trenaunay P. Du naevus variquex osteohypertrophique. *Arch Gen Med (Paris)*. 1900;3:641-672.
2. Bastarrika G, Redondo P, Sierra A, et al. New techniques for the evaluation and therapeutic planning of patients with Klippel-Trenaunay syndrome. *J Am Acad Dermatol*. 2007;56(2):242-249.
3. Cabrera J, Cabrera J Jr, García-Olmedo MA, Redondo P. Treatment of venous malformations with sclerosant in microfoam form. *Arch Dermatol*. 2003;139 (11):1409-1416.
4. Pascarella L, Bergan JJ, Yamada C, Mekenas L. Venous angiomata: treatment with sclerosant foam. *Ann Vasc Surg*. 2005;19(4):457-464.
5. McDonagh B, Sorenson S, Cohen A, et al. Management of venous malformations in Klippel-Trenaunay syndrome with ultrasound-guided foam sclerotherapy. *Phlebology*. 2005;20(2):63-81.
6. Nitecki S, Bass A. Ultrasound-guided foam sclerotherapy in patients with Klippel-Trenaunay syndrome. *Isr Med Assoc J*. 2007;9(2):72-75.
7. Cabrera J, Cabrera J Jr, inventors; BTG International Ltd, assignee. Injectable microfoam containing a sclerosing agent. European patent EP656203. June 21, 1993.
8. Cabrera J, Cabrera J Jr, inventors; BTG International Ltd, assignee. Injectable microfoam containing a sclerosing agent. US patent 5676962. October 16, 1997.
9. Paltiel HJ, Burrows PE, Kozakewich HP, Zurakowski D, Mulliken JB. Soft-tissue vascular anomalies: utility of US for diagnosis. *Radiology*. 2000;214(3):747-754.
10. Burrows PE, Mulliken JB, Fellows KE, Strand RD. Childhood hemangiomas and vascular malformations: angiographic differentiation. *AJR Am J Roentgenol*. 1983; 141(3):483-488.
11. Lee A, Driscoll D, Gloviczki P, Clay R, Shaughnessy W, Stans A. Evaluation and management of pain in patients with Klippel-Trenaunay syndrome: a review. *Pediatrics*. 2005;115(3):744-749.
12. Jacob AG, Driscoll DJ, Shaughnessy WJ, Stanson AW, Clay RP, Gloviczki P. Klippel-Trenaunay syndrome: spectrum and management. *Mayo Clin Proc*. 1998; 73(1):28-36.
13. Mazoyer E, Enjolras O, Laurian C, Houdart E, Drouet L. Coagulation abnormalities associated with extensive venous malformations of the limbs: differentiation from Kasabach-Merrit syndrome. *Clin Lab Haematol*. 2002;24(4):243-251.
14. Huiras EE, Barnes CJ, Eichenfield LF, Pelech AN, Drolet BA. Pulmonary thromboembolism associated with Klippel-Trenaunay syndrome [published online ahead of print September 15, 2005]. *Pediatrics*. 2005;116(4):e596-e600.

©2009 American Medical Association. All rights reserved.
Downloaded From: http://jamanetwork.com/ on 06/20/2013

15. de Lorimier AA. Sclerotherapy for venous malformations. *J Pediatr Surg*. 1995; 30(2):188-193, discussion 194.
16. Villavicencio JL. Primum non nocere: is it always true? the use of absolute ethanol in the management of congenital vascular malformations. *J Vasc Surg*. 2001; 33(4):904-906.
17. Yamaki T, Nozaki M, Sakurai H, Takeuchi M, Soejima K, Kono T. Prospective randomized efficacy of ultrasound-guided foam sclerotherapy compared with ultrasound-guided liquid sclerotherapy in the treatment of symptomatic venous malformations. *J Vasc Surg*. 2008;47(3):578-584.
18. Wollmann JCGR. The history of sclerosing foams. *Dermatol Surg*. 2004;30(5):694-703, discussion 703.
19. Cabrera J, Cabrera J Jr, García-Olmedo MA. Elargissement des limites de la sclerotherapie: nouveaux produits sclerosants. *Phlebologie*. 1997;2(4):181-188.
20. Cabrera J, Cabrera J Jr, García-Olmedo MA. Treatment of varicose long saphenous veins with sclerosant in microfoam form: long-term outcomes. *Phebology*. 2000;15(1):19-23.
21. Eckmann DM, Kobayashi S, Li M. Microvascular embolization following polidocanol microfoam sclerosant administration. *Dermatol Surg*. 2005;31(6):636-643.
22. Bikerman JJ. *Foams*. New York, NY: Springer-Verlag; 1973.
23. Redondo P, Cabrera J. Microfoam sclerotherapy. *Semin Cutan Med Surg*. 2005; 24(4):175-183.
24. Barrett JM, Allen B, Ockelford A, Goldman MP. Microfoam ultrasound-guided sclerotherapy of varicose veins in 100 legs. *Dermatol Surg*. 2004;30(1):6-12.
25. Yamaki T, Nozaki M, Iwasaka S. Comparative study of duplex-guided foam sclerotherapy and duplex-guided liquid sclerotherapy for the treatment of superficial venous insufficiency. *Dermatol Surg*. 2004;30(5):718-722.
26. Frullini A, Cavezzi A. Sclerosing foam in the treatment of varicose veins and telangiectases history and analysis of safety and complications. *Dermatol Surg*. 2002; 28(1):11-15.
27. Hsu TS, Weiss RA. Foam sclerotherapy: a new era. *Arch Dermatol*. 2003;139(11): 1494-1496.
28. Breu FX, Guggenbichler S. European consensus meeting on foam sclerotherapy, April 4-6, 2003, Tegernsee, Germany. *Dermatol Surg*. 2004;30(5): 709-717, discussion 717.
29. Regan JD, Gibson KD, Ferris B, et al. Safety of proprietary sclerosant microfoam for saphenous incompetence in patients with R-to-L shunt: interim report. *J Vasc Interv Radiol*. 2008;19(suppl 2):S35.
30. Kerns SR, Hawkins IF Jr. Carbon dioxide digital subtraction angiography: expanding applications and technical evolution. *AJR Am J Roentgenol*. 1995; 164(3):735-741.
31. Meier B, Lock JE. Contemporary management of patent foramen ovale. *Circulation*. 2003;107(1):5-9.
32. Ceulen RPM, Sommer A, Vernooy K. Microembolism during foam sclerotherapy of varicose veins. *N Engl J Med*. 2008;358(14):1525-1526.
33. Passariello F. Sclerosing foam and patent foramen ovale: the final report. *Int Angiol*. 2007;26(suppl 1):87.
34. Guex JJ, Raymond-Martimbeau P, Simka M, Passariello F. Letter regarding article titled "Microembolism during foam sclerotherapy of varicose veins" in the *New England Journal of Medicine. Phlebology*. 2008;23(5):249-250.
35. Forlee MV, Grouden M, Moore DJ, Shanik G. Stroke after varicose veins foam injection sclerotherapy. *J Vasc Surg*. 2006;43(1):162-164.
36. Schaefer PW. Applications of DWI in clinical neurology. *J Neurol Sci*. 2001;186 (suppl 1):S25-S35.
37. Rush JE, Wright DDI. More on microembolism and foam sclerotherapy. *N Engl J Med*. 2008;359(6):656-657, author reply 657.

©2009 American Medical Association. All rights reserved.
Downloaded From: http://jamanetwork.com/ on 06/20/2013