

LIQUID NITROGEN CRYOTHERAPY FOR CONJUNCTIVAL LYMPHANGIECTASIA: A CASE SERIES

BY Frederick W. Fraunfelder MD*

ABSTRACT

Purpose: To report a case series of conjunctival lymphangiectasia treated with liquid nitrogen cryotherapy.

Methods: A 1.5-mm Brymill cryoprobe was applied in a double freeze-thaw method after an incisional biopsy of a portion of the conjunctiva in patients with conjunctival lymphangiectasia. Freeze times were 1 to 2 seconds with thawing of 5 to 10 seconds between treatments. Patients were reexamined at 1 day, 2 weeks, 3 months, 6 months, and yearly following cryotherapy.

Results: Five eyes of 4 patients (3 male and 1 female) with biopsy-proven conjunctival lymphangiectasia underwent liquid nitrogen cryotherapy. The average patient age was 53 years. Ocular examination revealed large lymphatic vessels that were translucent and without conjunctival injection. Subjective symptoms included epiphora, ocular irritation, eye redness, and occasional blurred vision. After treatment with liquid nitrogen cryotherapy, the patients' symptoms and signs resolved within 2 weeks. Lymphangiectasia recurred twice in one patient, at 1 and 3 years postoperatively. In another patient, lymphangiectasia recurred at 6 months. The average time to recurrence in these 3 eyes was 18 months. Average length of follow-up was 24.5 months for all subjects.

Conclusion: Liquid nitrogen cryotherapy may be an effective surgical alternative in the treatment of conjunctival lymphangiectasia. Cryotherapy may need to be repeated in some instances.

Trans Am Ophthalmol Soc 2009;107:229-233

INTRODUCTION

Conjunctival lymphangiectasia is characterized by dilated and prominent lymphatic channels within the conjunctiva. The condition is usually unilateral unless associated with Turner syndrome or Nonne-Milroy-Miege disease. Symptoms may include ocular irritation, dryness, epiphora, blurred vision, and pain.¹ The terms *lymphangiectasia* and *lymphangioma* are used interchangeably, and if there is bleeding into the lymph channels, the condition is called hemorrhagic lymphangiectasia.²

The etiology of lymphangiectasia is unknown. Simple excision or marsupialization, or both, are therapeutic options described to treat this condition.^{3,4} A case series of conjunctival lymphangiectasia treated with liquid nitrogen cryotherapy has not been reported.

METHODS AND MATERIALS

Four patients presented to the Casey Eye Institute, Portland, Oregon, with epiphora, eye irritation, eye redness, and episodic blurred vision. Ocular examination of the 5 affected eyes revealed swelling of the conjunctiva with transparent lymphangiectatic vessels on the globe.

Prior to cryotherapy, an incision was made in the involved conjunctiva with 0.12-mm forceps and sharp Westcott scissors (Figure 1). A 1- to 2-mm² portion of tissue was excised and sent to pathology in formalin for pathologic diagnosis (Figure 2). In each case, the clinical suspicion of conjunctival lymphangiectasia was confirmed by the ophthalmic pathologist's description of noninflamed large lymphatic vessels. After the incisional biopsy, a single 6-0 fast gut suture was placed.

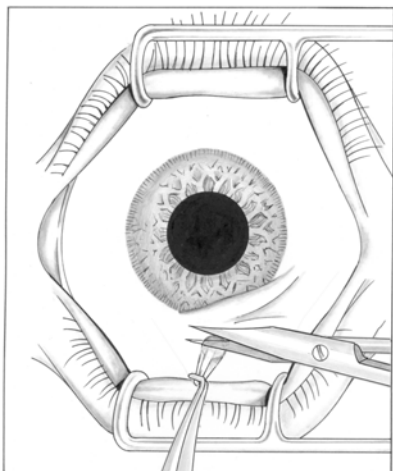


FIGURE 1

Tenting of the redundant conjunctiva prior to an incisional biopsy with Westcott scissors.

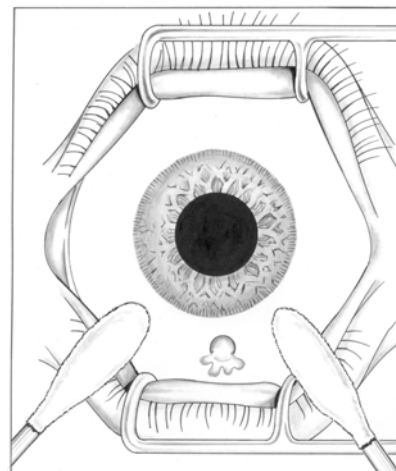


FIGURE 2

Cotton swab–assisted expression of subconjunctival fluid.

*Presenter.

Bold type indicates AOS member.

From Casey Eye Institute, Oregon Health and Science University, Portland, Oregon.

Liquid Nitrogen Cryotherapy for Conjunctival Lymphangiectasia

Cryotherapy was performed using a Brymill Cry-Ac-3 liquid nitrogen unit (Brymill Cryogenic Systems, Ellington, Connecticut). Various probes can be attached to the unit, depending on the disease and the surface being frozen. A 1.5-mm Teflon-coated cryoprobe was used for treatment in this case series (Figures 3 and 4). Since the boiling point of liquid nitrogen is -195.6°C , allowing the cryoprobe tip to freeze until the frost around the probe liquefies (approximately 15 seconds) confirms that the lowest temperature of liquid nitrogen has been reached. A double freeze-thaw technique was used, whereby the cryoprobe was left in contact with the conjunctiva for 1 to 2 seconds in 2 freeze-thaw cycles. Thaw time takes approximately 5 to 10 seconds.

Erythromycin eye ointment was placed on the eye after the procedure. Patients were seen for follow-up examinations at 1 day, 2 weeks, 3 months, 6 months, and yearly thereafter.

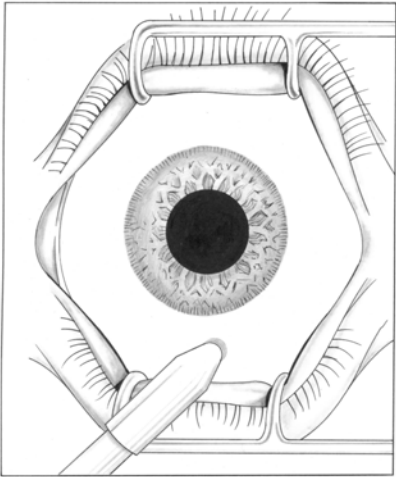


FIGURE 3

Liquid nitrogen cryotherapy with 1.5-mm cryoprobe.

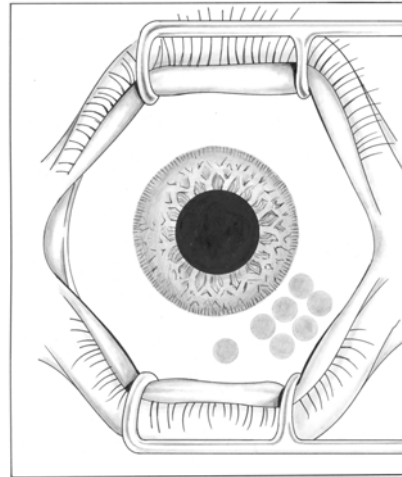


FIGURE 4

Multiple areas of cryotherapy applied over the conjunctival lymphangiectasia

RESULTS

Five eyes of 4 patients (3 male and 1 female) with biopsy-proven conjunctival lymphangiectasia underwent liquid nitrogen cryotherapy. The symptoms and signs of conjunctival lymphangiectasia resolved within 2 weeks after treatment in all 5 eyes treated. The average patient age was 53 years, and average length of follow-up was 24.5 months. There were 2 recurrences in this case series: the first was at 1 and 3 years in the same eye of the same patient (patient 1), and the second at 6 months in a different patient (patient 3) (Table). Average time to recurrence of conjunctival lymphangiectasia was 18 months. Repeated cryotherapy led to resolution of recurrent conjunctival lymphangiectasia in all patients treated (Figure 5).

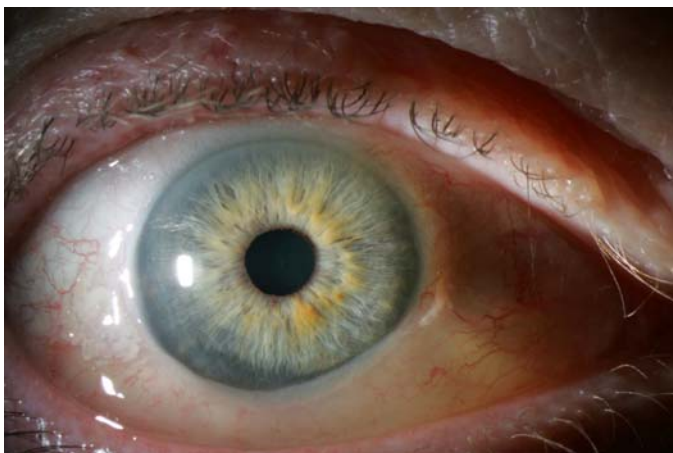


FIGURE 5

Patient 2 (see Table). Left, Conjunctival lymphangiectasia prior to treatment. Right, Same eye 6 months after treatment with liquid nitrogen cryotherapy.

TABLE. CONJUNCTIVAL LYMPHANGIECTASIA TREATED WITH LIQUID NITROGEN CRYOTHERAPY

PATIENT	AGE (YR)	GENDER	EYE TREATED	TIME TO RECURRENCE	RE-TREATMENT	LENGTH OF FOLLOW-UP
1	57	Male	OS	1 yr and 3 yr	Yes ×2	5 yr
2	64	Male	OD	NA	None	2 yr
3	44	Male	OS	6 mo	Yes ×1	6 mo
4	46	Female	OU	NA	None	6 mo

NA, not applicable.

DISCUSSION

Liquid nitrogen cryotherapy is effective in treating conjunctival lymphangiectasia most likely by collapsing the lymph vessel walls onto each other by a cryogenic burn. Another probable mechanism is scarring down the conjunctiva to the underlying globe. By creating an adhesion between the superficial conjunctiva and underlying Tenon capsule and sclera, the symptoms and signs of this condition are minimized. In addition, cryotherapy has been shown to kill endothelium of blood vessels, and it would make sense that the endothelium lining the large lymphatic vessels in this condition is also damaged through the cryogenic burn.⁵

Alternative treatments for conjunctival lymphangiectasia have been described. Surgical excision alone was described in a case series by Meisler and associates.⁶ In their series, 3 eyes had conjunctival resection without recurrence after 2 years of follow-up. The difference between that series and the series described in this report is that only a small portion of conjunctiva was excised prior to cryotherapy in the current series, as opposed to all of the conjunctiva involved with lymphangiectasia in the series of Meisler and associates.

In a case report by Jordan and coworkers,⁷ a carbon dioxide laser was used to successfully treat what was described as a conjunctival lymphangioma. Behrendt and colleagues⁸ used beta-irradiation to successfully treat a case of conjunctival lymphangioma. A case report from Egypt by Wasfy⁹ describes the use of cryotherapy to successfully treat a case of conjunctival lymphangiectasia, although the type of cryogen and the technique are not explained.

Liquid nitrogen cryotherapy has been proven safe and effective for conjunctival malignancies,¹⁰⁻¹² and it also appears to be efficacious in the treatment of multiple other ocular conditions, including benign conjunctival vascular tumors,⁵ advancing wavelike epitheliopathy,¹³ superior limbic keratoconjunctivitis,¹⁴ pterygia,¹⁵ and conjunctival amyloidosis.¹⁶

Based on this case series, liquid nitrogen cryotherapy using the surgical technique described could be considered an effective surgical alternative in the treatment of conjunctival lymphangiectasia. Subsequent cryotherapy may be indicated should lymphangiectasia recur.

ACKNOWLEDGMENTS

Funding/Support: This study was supported in part by an unrestricted grant to Casey Eye Institute from Research to Prevent Blindness, New York, New York.

Financial Disclosures: Dr Fraunfelder is a consultant for Brymill and Ono Pharmaceuticals.

Conformity With Author Information: This study was given an exemption from full board approval by the IRB. The study conformed to the Tenets of Helsinki.

REFERENCES

- Perry HD, Cossari AJ. Chronic lymphangiectasis in Turner's syndrome. *Br J Ophthalmol* 1986;70:396-399.
- Jampol LM, Nagpal KC. Hemorrhagic lymphangiectasia of the conjunctiva. *Am J Ophthalmol* 1978;85:419-420.
- Spraul CW, Buchwald HJ, Lang GK. Idopathic conjunctival lymphangiectasia. *Klin Monatsbl Augenheilkd* 1997;210:398-399.
- Shields JA, Shields CL. Lymphangiectasia and lymphangioma. In: *Atlas of Eyelid and Conjunctival Tumors*. Philadelphia: Lippincott Williams & Wilkin; 1999:270-271.
- Fraunfelder FW, Fraunfelder FT. Liquid nitrogen cryotherapy of a conjunctival vascular tumor. *Cornea* 2005;24:116-117.
- Meisler DM, Eiferman RA, Ratliff NB, Burns CD. Surgical management of conjunctival lymphangiectasis by conjunctival resection. *Am J Ophthalmol* 2003;136:735-736.
- Jordan DR, Anderson RL. Carbon dioxide (CO₂) laser therapy for conjunctival lymphangioma. *Ophthalmic Surg* 1987;18:728-730.

8. Behrendt S, Bernsmeier H, Randzio G. Fractionated beta-irradiation of a conjunctival lymphangioma. *Ophthalmologica* 1991;203:161-163.
9. Wasfy IA. Lymphangiectasia haemorrhagica conjunctivae: report of three cases with a note on successful treatment with cryosurgery in one case. *Bull Ophthalmol Soc Egypt* 1975;68:37-44.
10. Eichler MD, Fraunfelder FT. Cryotherapy for conjunctival lymphoid tumors. *Am J Ophthalmol* 1994;118:463-467.
11. Jakobiec FA, Rini FJ, Fraunfelder FT, Brownstein S. Cryotherapy for conjunctival primary acquired melanosis and malignant melanoma. Experience with 62 cases. *Ophthalmology* 1988;95:1058-1070.
12. Fraunfelder FT, Wingfield D. Management of intraepithelial conjunctival tumors and squamous cell carcinomas. *Am J Ophthalmol* 1983;95:359-363.
13. Fraunfelder FW. Liquid nitrogen cryotherapy of advancing wavelike epitheliopathy. *Cornea* 2006;25:196-198.
14. Fraunfelder FW. Liquid nitrogen cryotherapy of superior limbic keratoconjunctivitis. *Am J Ophthalmol* 2009;147:234-238.
15. Fraunfelder FW. Cryotherapy for pterygia. *Ophthalmology* 2008;115:2314-2314.
16. Fraunfelder FW. Liquid nitrogen cryotherapy for surface eye disease (an American Ophthalmological Society thesis). *Trans Am Ophthalmol Soc* 2008;106:301-324.

PEER DISCUSSION

DR. JAMES CHODOSH: As described by Duke Elder,¹ conjunctival lymphangiectasia has two principal manifestations: a cystic lesion of the conjunctiva which may mimic allergic chemosis,² and a beaded dilatation of lymphatic vessels with a string of pearl appearance. Unless the latter type acquires communication with a conjunctival vein and becomes hemorrhagic, simple dilatations of the conjunctival lymphatics are asymptomatic and usually unnoticed. Diffuse unilateral lymphangiectasia can occur after surgical lymph node dissection in head and neck cancer. Bilateral lymphangiectasia can be associated with familial lymphedema and Turners syndrome.³ Lymphangiectasia can lead to irritation and redness from desiccation of the overlying conjunctival epithelium, and epiphora, if the lacrimal puncta become functionally occluded by overhanging conjunctiva. However, lymphangiectasia, which by histopathology represents an abnormal dilatation of endothelial cell lined conjunctival lymphatic vessels in the absence of inflammation,⁴ is generally considered a minor disorder.

Fraunfelder reports 5 eyes of 4 patients with biopsy proven conjunctival lymphangiectasia and associated ocular symptoms that were treated with liquid nitrogen cryotherapy. Resolution of signs and symptoms occurred within 2 weeks of treatment in all 5 eyes. After an average of 2 years follow-up, 3 of the 5 eyes had developed recurrent lesions, with an average time to recurrence of 18 months. Repeat cryotherapy led to resolution in all cases, although the length of follow-up was not reported. Although cryotherapy would appear to be less invasive than surgical excision, it remains unclear from this report which method is least likely to lead to recurrence of lymphangiectasia. Such reports raise the question of how we should determine the best therapy in uncommon conditions.

ACKNOWLEDGMENTS

Funding/Support: None

Financial Disclosures: None

REFERENCES

1. Duke-Elder S. Conjunctival diseases. In: *Diseases of the Outer Eye, Part 1*. Vol. VIII, St. Louis: Mosby: 1965:40.
2. Kalin NS, Orlin SE, Wulc AE, et al. Chronic localized conjunctival chemosis. *Cornea* 1996;15:295-300.
3. Perry HD, Cossari AJ. Chronic lymphangiectasis in Turner's syndrome. *Br J Ophthalmol* 1986;70:396-399.
4. Watanabe A, Yokoi N, Kinoshita S, Hino Y, Tsuchihashi Y. Clinicopathologic study of conjunctivochalasis. *Cornea* 2004;23:294-298.

DR. ALLAN J. FLACH: It was interesting. Rick, why do you use such a large cryoprobe? The size of it was sort of surprising.

DR. EDUARDO C. ALFONSO: I have no financial interest. Would you consider doing impression cytology before and after treatment? It looks like you are getting rid of many goblet cells and patients may end up years later with significant dry eye syndrome from this condition. For treatment of this condition in similar eyes, I have lifted the conjunctiva and removed all of the underlying subconjunctival stromal Tenon's tissue where the lymphatics are located to preserve the surface epithelium. A second question, have you measured the actual temperature that you are exposing the eye to in the interest of finding out what other intraocular structures could potentially be affected?

DR. MALCOLM R. ING: No financial conflict. I would like your opinion about whether or not this therapy might be beneficial in the treatment of the rare conjunctival epithelial cyst that develops after strabismus surgery. Have you had the opportunity to treat that condition?

DR. FREDERICK W. FRAUNFELDER: Thank you to Dr. Chodosh for being merciful. The question that he posed during the discussion was if the recurrence was less severe. In every instance one of the features that sells this surgery to me and to my fellows is that the patients are so happy. Even if it recurs they are anxious to come back and to undergo another treatment because it is less severe and they are hopeful that the condition can only get better if we treat it again. On average the patients saw about 5 doctors before I initially examined them. It is very gratifying to offer a surgical option for a condition that usually has bothered them for many years.

It is a rare condition and I am faced with that whenever I perform cryotherapy on some of these rare conditions, such as conjunctival amyloidosis, conjunctival sarcoidosis, and advancing wave-like epitheliopathy. It is difficult to accumulate 100 cases of this type in your practice, so I am not sure how to formulate an answer other than on the basis of this kind of case series. One idea would be to spread the surgical technique around other centers and that is what we are doing is training our fellows. We now have three fellows throughout the country who are also performing cryotherapy for the treatment of these diseases. In the future hopefully we will have more case reports on this treatment.

Dr. Flach asked about the cryoprobe size. The dimension of the cryoprobe is 2 mm. I do have the choice of using a smaller, 1mm probe, and there are even some pinpoint type cryoprobes. I am attempting to produce a larger freeze because, as Dr. Chodosh pointed out, this is a diffuse condition and you do not know where it begins or ends. The condition probably reoccurs because I have not treated an area with lymphangiectasia located elsewhere.

Dr. Alfonso talked about inducing dry eye and it is a very good point. One of the side effects of aggressive cryotherapy is a chronic dry eye. Typically, though, if you freeze just a section of the globe, perhaps just one quadrant and not the whole globe, this has not been a chronic problem for the patients whom I have treated. The temperature of the tissue has been measured. It has not been measured by me in these experiments because it has been done prior to me by my betters. The thermal couple experiments were performed by Dr. Fraunfelder, Sr., that showed that if you maintain cryoprobe contact with the eye for three to five seconds or less, then the freeze is very superficial, in the range of about 30-40 microns deep. We are not affecting the uvea or the retina if we are freezing for a very short time. For conjunctival cysts, I have never treated that condition, but it is a great idea. I am certain that if you marsupialize the cyst and then perform cryotherapy the cyst would scar on itself and not recur. Thank you.