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REVIEW

Ablative laser assisted topical delivery of antifibrotics in the management of cicatricial ectropion

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Abstract

A variety of surgical techniques have traditionally been used to manage cicatricial ectropion. These techniques primarily aim at vertical lengthening of the anterior lamella and include a variety of skin flaps and grafts. Alternative techniques such as dermal filler injection to support the eyelid margin may also be used in the management of select patients with cicatricial ectropion. The application of different types of laser for scar revision throughout the body has rapidly evolved; similar mechanisms, principles and treatment rationale can be applied to the use of lasers in the management of cicatricial ectropion. Additionally, ablative lasers, such as Carbon Dioxide and Erbium:yttrium-aluminum-garnet lasers, may be used in the transdermal delivery of antifibrotic agents, such as interferon gamma, interferon alpha, vitamin D, triamcinolone and 5-fluorouracil, resulting in efficient target tissue penetration, limitation of systemic drug toxicity and decreased degradation. Although the combination of ablative fractional resurfacing and topical antifibrotic agents is a new treatment modality, there is a great potential for its efficient utility in the management of periocular scarring and cicatricial ectropion. The introduction of these innovative therapeutic modalities offers ophthalmologists a greater range of possible effective treatments to address periocular scar tissue and the resultant cicatricial ectropion.

Key words: Laser; Antifibrotic agents; Cicatricial ectropion; Periocular scarring; Ablative fractional resurfacing

Core tip: There is a broad range of conservative as well as more invasive treatment modalities for cicatricial ectropion. Ablative lasers can be used alone or in conjunction with nonablative lasers in the treatment of periocular scarring and cicatricial ectropion. Additionally, they may be used to assist the transdermal delivery of antifibrotic agents. This treatment modality, although still uncommonly used to treat periocular scarring, is a promising new technique that offers many advantages. Ophthalmologists may utilize this technique to manage cicatricial ectropion.

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INTRODUCTION

Cicatricial ectropion presents a formidable clinical challenge; sequelae range from redness, tearing and foreign body sensation to potentially devastating complications, including corneal scarring, ulceration, perforation, and permanent vision loss.

Eyelid eversion is usually secondary to relative shortening of the anterior lamella. A broad range of etiologies

has been reported, but the most common include excision of cutaneous malignancy, prior lower lid blepharoplasty, thermal or chemical burns, and actinic damage in fair-skinned Caucasians[1,2]. Less commonly, cicatrizing skin diseases such as lamellar ichthyosis, scleroderma, neurodermatitis, pyoderma gangrenosum, and Grzybowski-type keratoacanthoma may be implicated[3-5]. Drug related cicatricial changes, including those caused by glaucoma drops and chemotherapeutic agents, generally resolve following discontinuation of the offending agent, but occasionally require additional interventions[6,7]. Tethering within the middle lid lamella, which includes the orbital septum, retractors and preaponeurotic fat, is also a potential cause of cicatricial ectropion, and usually occurs as the result of trauma or prior surgery.

When treating cicatricial ectropion, it is necessary to understand the fundamentals of the wound healing process. Scar formation results from mechanical, chemical or thermal insults to the deep dermis. This initiates a wound-healing cascade that progresses through inflammatory, proliferative and remodeling/maturation phases[8,9]. During the inflammatory phase, platelet activation and degranulation releases cytokines and growth factors that result in the formation of a fibrin clot, which acts as an initial scaffold for repair. This is followed by chemotaxis of macrophages, neutrophils and fibroblasts. Fibroblast growth factor 2 (FGF-2), transforming growth factor (TGF)-β and insulin like growth factor produced by macrophages then induce neocollagenesis. Fibroblasts synthesize extracellular matrix (ECM), which permits vascular ingrowth. Myofibroblasts participate in wound contracture. During the maturation phase, which can take up to two years, the ECM is degraded by matrix metalloproteinases (MMPs) and type Ⅲ collagen is replaced by a more orderly array of type I collagen[8].

There is little systematic documentation in the ophthalmic literature regarding the demographic characteristics of patients with clinically significant cicatricial ectropion. Reviewing the records of 145 patients undergoing skin grafts at the Duke Eye center, Ehrlich *et al*[10] found a male preponderance and a mean age of 75 years. Thirty five percent had undergone prior transcutaneous lower eyelid blepharoplasty, 20% had a history of Mohs reconstruction, 10% a history of facial trauma, and 5% had systemic cicatrizing diseases such as scleroderma. In 45% of patients, however, the etiology was unknown.

TRADITIONAL SURGICAL MANAGEMENT

Management typically begins with conservative measures such as massage, topical emollients or steroids, and aggressive lubrication of the ocular surface. Even if further interventions are anticipated, it can be helpful to moisten the dry and keratinized palpebral conjunctiva for a few weeks prior to restoring contact with the ocular surface.

Surgical repair is aimed at vertical lengthening of the deficient anterior lamella, but may also incorporate ancillary measures to reduce the likelihood of recurrence, such as horizontal tightening, lid retractor reinsertion, and suborbicularis oculi lift[2,11]. Depending on the etiology of ectropion, lysis of middle lamellar adhesions may also be necessary. Traditional techniques include transposition flaps from the opposing eyelid, full-thickness skin grafts (FTSGs), W- and Z-plasty with scar excision, and island flaps based on the superficial temporal artery[12].

Bipedicle myocutaneous upper to lower eyelid transposition flaps generally offer the best color and texture match. They have been subject to multiple refinements since introduced by Landolt in 1885[11,13]. A bipedicle flap has several distinct advantages over a temporally hinged unbipedicle flap including improved blood supply and improved structural support as it acts as a sling from the upper eyelid[11,13].

FTSGs are also a popular option for anterior lamellar augmentation. Matching of skin color, texture and thickness is critical to optimizing cosmetic and functional outcomes. The suitability of tissues, in descending order, includes the upper eyelid, preauricular area, postauricular area, and supraclavicular region[14]. Lack of suitable donor tissue remains the primary contraindication; burn patients and those with systemic cicatrizing conditions may be poor candidates. Given the prevalence of robust collaterals in the eyelids, necrosis and infection are rare complications. Careful hemostasis and use of postoperative bolsters, however, are necessary to reduce the risk of hematoma formation, which can rapidly devitalize a graft.

Z-plasty is useful for addressing cicatricial ectropion, but is limited to cases resulting from focal scarring. It is typically combined with scar excision or minimization. W-plasty is a related revision technique that creates a regularly irregular wound in lieu of a straight one, lengthening parallel to the original scar. Increased skin tension contributes to further hypertrophic scarring, creating a vicious cycle that can be broken by these revision techniques[9].

ALTERNATIVE TECHNIQUES

Systemic cicatrizing disease may limit the availability of viable autograft tissues. Some authors report use of groin or even penile foreskin in the setting of limited donor sites[4,15,16]. More radical departures, such as grafting mucus membranes, maternal skin, and even human skin replacements, have been described[15,17,18].

Hyaluronic acid fillers have also been used to treat select cases of cicatricial ectropion. It is thought that the filler volume physically supports the eyelid margin and acts as an injectable tissue expander, stretching the tethered anterior lamella[1]. It may be an attractive alternative in older, debilitated patients and those not desiring further surgical intervention.

APPLICATION OF LASERS FOR SCAR REVISION AND CICATRICIAL RELEASE

Laser therapy has rapidly evolved into a valuable treatment modality to improve the appearance and physical properties of cutaneous scar tissue throughout the body.

Table 1 Fitzpatrick sun reactive skin types

Skin phototypes	Sunburn	Tan
Type Ⅰ	Yes	No
Type Ⅱ	Yes	Minimal
Type Ⅲ	Yes	Yes
Type Ⅳ	No	Yes
Type Ⅴ	No	Yes
Type Ⅵ	No	Yes

The principles and treatment rationale for laser treatment of scars can also be extended to the treatment of cicatricial ectropion.

Selection of treatment candidates

Prior to proceeding with laser therapy for scar revision, several factors that are individual to each patient need to be considered. First, the patient's skin type is determined-with a classification scheme such as the Fitzpatrick scale (Table 1)-in order to stratify the patient in terms of appropriate laser settings and possible risks and side effects of laser therapy[19]. Greater skin pigmentation results in increased interference of the energy delivered by the laser, thus decreasing the amount delivered to the targeted hemoglobin and therefore the dermal scar tissue. Additionally, patients with darker skin types are at greater risk of melanin destruction which leads to postoperative skin dyspigmentation[20-22].

Caution should also be taken in patients with inflammatory, autoimmune, or infectious skin disorders. Dermal inflammation of any etiology may interfere with postoperative healing and therefore decrease the overall effectiveness of the laser treatment. Patients may experience exacerbation or dissemination of autoimmune (*e.g.*, vitiligo, lupus) or inflammatory (*e.g.*, psoriasis, eczema) conditions after laser therapy. Additionally, 0.5% to 4.5% of patients undergoing ablative laser treatment can experience exacerbation of disseminated skin infections (*e.g.*, herpes simplex virus, impetigo, mollusum, verruca)[20-22]. It has been recommended that prophylactic oral antiviral agents be administered in patients with a history of perioral herpes simplex one day before treatment and continued one week after treatment[20,22], although most physicians treat patients regardless of history if using ablative therapy.

The patient's current and previous medication usage should also be reviewed prior to initiating laser therapy. Isotretinoin and other common medications may lead to development of hypertrophic scars. Anticoagulants and antiplatelet agents should be discontinued one week prior to treatment to decrease the amount of post-treatment bruising[21].

Additional caution should be exercised in patients who have undergone previous treatments such as chemical peels, dermabrasion, or dermal filler injections[21].

Selection of laser and application

In general, lasers used for scar tissue remodeling can be divided into two major categories: ablative and nonablative (Table 2)[23,24]. Ablative lasers [*e.g.*, Erbium:yttrium-aluminum-garnet (Er:YAG) 2940 nm, CO_2 10600 nm] have a high affinity for water and causes thermal necrosis as the energy is absorbed by scar tissue. Application of this type of laser also results in an increased level of basic FGF and reduces TGF-β1, which theoretically decreases re-contraction of scars[25,26]. Treatment with this laser induces scar remodeling and improves atrophy, contracture, and texture of existing scar tissue. Commonly experienced side effects after treatment include pain, post-treatment erythema, transient and permanent hyperpigmentation, and infection[26,27]. The Er:YAG laser has a higher affinity for water than the CO_2 laser, and therefore patients typically experience less severe side effects[27].

Nonablative lasers [*e.g.*, 532-nm or 1064-nm neodymium:YAG (Nd:YAG), 585-nm pulsed-dye laser (PDL)] are chromophore-selective (*e.g.*, hemoglobin and melanin), and are thus selectively absorbed without inflicting widespread damage to surrounding tissues[27,28]. Application of the 532-nm neodymium YAG laser and 585-nm PDL results in absorption of energy by the hemoglobin, which has an absorption peak of 542-nm, that is present within the scar microvasculature. This results in ischemia, thrombosis, coagulation necrosis, and decreased collagen within the scar. At this wavelength, the laser energy is also selectively absorbed by melanin, which causes decreased scar hyperpigmentation. Additional benefits include decreased proliferation of fibroblasts[29] and deposition of collagen Ⅲ. Similar to ablative lasers, PDL also decreases TGF-β1. Nd:YAG laser treatments also causes suppression of collagen production. Treatment with nonablative lasers results in improvement of scar texture and pliability[29]. Commonly experienced side effects after treatment include post-treatment purpura and skin dyspigmentation[27].

Although there are no standard algorithms for laser treatment of cicatricial ectropion, a general approach similar to that used in treating scar tissue present in other areas of the body may be followed. In general, scar tissue is first treated with a laser that targets the microvascular component of scar tissue, which destroys the vessels and decreases the inflammation.

Next, laser energy that targets water is used to destroy and remodel the abnormal collagen fibers. Previously, ablative lasers were used to vaporize tissues at a consistent and superficial depth. However, these lasers are now typically applied in a fractional pattern, which results in the ablation of deep columns of abnormal scar tissue [microscopic thermal zones (MTZ)] that are intermixed within islands of untreated normal tissue[20]. This not only allows for a quicker recovery through rapid reepithelization and cell migration from the surrounding tissue with retained adnexal structures[30,31], it also changes collagen by modulating interleukin-1, tumor necrosis factor, TGF, heat shock proteins, and MMP. This results in the clearance of damaged collagen and the proliferation, migration, and differentiation of keratinocytes in wounds that result in the formation of new healthy collagen, resulting in more organized scar tissue with physical properties

Table 2 Common types of ablative and non-ablative lasers

	Wavelength	Manufacturer	Product name
Ablative laser			
CO_2	10600 nm	Sandstone medical technologies	Matrix LS-40
		Lumenis	UltraPulse
		Lumenis	AcuPulse
Er:YAG	2940 nm	Focus medical	NaturaLase ER
		Alma lasers gmbh/quantel derma	Burane
		Sandstone medical technologies	Whisper 3-G
		Sciton	Contour TRL
		Syneron and candela	SmoothPeel
Combined CO_2 Er:YAG laser	10600 nm/2940 nm	Sandstone medical technologies	Sandstone medical technologies cortex resurfacing work station
Nonablative laser			
Infrared range			
Pulsed energy	1319 nm	Sciton	Thermascan
Nd:YAG	1320 nm	CoolTouch	CT3Plus
		Alma lasers	Harmony XL
Diode	1450 nm	Syneron and candela	Smoothbeam
Er:Glass	1540 nm	Alma lasers	ARAMIS
Visible range			
Pulsed dye laser	585 nm/532 nm	Chromogenex	Regenlite
		Cynosure	V-Star
Long pulsed	532 nm	Laserscope aura	StarPulse
		Lumenis	VersaPulse

CO_2: Carbon dioxide; Er:YAG: Erbium:yttrium-aluminum-garnet; Nd:YAG: Neodymium:yttrium-aluminum-garnet; Er:Glass: Erbium:Glass.

and function that is more comparable to the surrounding healthy tissue[32-34].

An alternative method of treatment using the ablative CO_2 laser includes the pinhole method, where multiple small holes are made in regular intervals within the scar tissue. The delivery of focal laser energy results in a softening effect by breaking down the thick and irregular collagen bundles and may promote to more structured deposition of collagen and elastin[35]. Similar to the fractional pattern method, there is also migration of epithelial cells from surrounding viable tissue.

When using laser for the treatment of cicatricial ectropion, one should keep in mind that the eyelid skin is very thin and fragile so treatment density and power need to be greatly reduced[26] to avoid further damage of periorbital skin. In fact, cicatricial ectropion has also been reported as a complication of fractional CO_2 laser treatment and it should be used with caution in patients with a history of previous eyelid surgery or limited skin elasticity[22].

LASER ASSISTED DRUG DELIVERY

In addition to being used alone or in conjunction with nonablative lasers for treatment of cicatricial ectropion, ablative lasers may also be used in the delivery of therapeutic molecules. Although this is not a common treatment for cicatricial ectropion, the application of principles and treatment rationale for treatment of scar tissue present in other areas of the body can be used to guide treatment of periocular scar tissue.

Compared to systemic therapy, transdermal delivery of therapeutic agents has the advantages of directly targeting the affected organ, limitation of systemic toxicity, decreased drug degradation, and bypass of metabolism by the gastrointestinal and hepatic system. In order to achieve effect, the agent must penetrate the epidermis. The main barrier and rate-limiting step to drug penetration into the skin is the stratum corneum of the epidermis, which is composed of hydrophilic corneocytes arranged within lamellar sheets of hydrophobic lipid matrix. Once penetration is achieved, diffusion of the therapeutic agent encounters less resistance through the dermis (which is composed of collagen, glycosaminoglycans, and elastic fibers) and underlying subcutaneous tissue[36,37].

Principles of ablative laser use in conjunction with topical therapeutic agents

Ablative lasers applied in a fractional pattern [*i.e.*, ablative fractional resurfacing (AFR)] can be used to create vertical columns of ablated tissue at various depths. The two main lasers used for this task include the CO_2 laser and Er:YAG lasers mentioned previously in this article. The CO_2 laser creates a thicker MTZ when compared to the Er:YAG, but for both lasers the end result is the creation of regular strips of MTZs interspersed between areas of untreated skin containing appendageal units[38]. Histological studies of treated tissue have demonstrated MTZs with diameters up to 100 μm and depths up to 300 μm[39], but laser channels can be set to reach depths much greater than this. Therefore, AFR enhances transdermal delivery of therapeutic agents by disrupting the barrier function of the epidermis while allowing for rapid recovery through migration of epithelial cells from the surrounding untreated areas of skin.

The delivery of topical therapeutic agents can be augmented by adjustment of variables such as channel density and depth. Cumulative permeability of different

therapeutic agents has been studied and shows that for a fixed area of skin and fluence, an increase in the number of channels resulted in increased cumulative permeation. However, there was a nonlinear relationship between cumulative permeation and the number of MTZ channels. Within a given dosing time interval, there is a minimum number of channels required to achieve a targeted drug permeation and creating a greater number of channels will not exert a greater clinical effect[40,41].

MTZ channel depth is controlled by adjusting fluence. As expected, a greater fluence results in greater energy delivered per unit area, which results in a greater depth of penetration[40]. Thus, modulation of fluence can be used to target more superficial *vs* deeper areas of the skin. Although one would expect that cumulative permeation is directly proportional to depth of penetration due to increased exposed surface area for absorption, this has not been shown to be true in *in vivo* studies[41,42]. Oni *et al*[42] used a porcine model to demonstrate that serum levels of lidocaine and its metabolite monoethylglycinexylidide did not show a positive correlation with channel depth. At given time intervals, peak levels were significantly higher at a depth of 250 μm compared to 25, 50, and 500 μm. It has been hypothesized that the depth at which vascular plexuses are located within the tissue play a significant role in drug absorption[42]. Therefore, treatment should be tailored to the anatomical locations of vascular plexus contained within different areas of the skin.

Additional factors that may affect topical drug delivery include diffusion area of each drug from the MTZ channel in which it initially penetrated. This would require a calculation of the number and spacing of channels needed to cover any given area. For example, *in vitro* studies showed that methyl 5-aminolevulinate, a sensitizer in photodynamic therapy, diffuses 1.5 mm from each laser channel[38]. However, the distance of diffusion is likely related to physical properties (such as molecular weight, molecular size, and lipophilicity) of the drug molecule itself, and would need to be empirically determined for each therapeutic agent[37,43].

Candidate drugs for ablative laser assisted topical delivery

The use of antifibrotics in the management and treatment of cicatricial ectropion is still in its infancy and not widely practiced. Conceptually, it is a promising treatment option and warrants further investigation. Antifibrotic agents used to treat scar tissue in other areas of the body, such as interferon gamma, interferon alpha, corticosteroids, and vitamin D are theoretically good candidates for AFR assisted topical delivery[36]. Waibel *et al*[44] demonstrated that AFR assisted topical delivery of triamcinolone (TAC) greatly improved texture in hypertrophic cutaneous scars. It is likely that similar effects would be achieved with cicatricial ectropion.

The technique of AFR assisted topical delivery of therapeutic agents also opens a unique opportunity for localized delivery of unstable agents such as proteins. Local immunosuppressive effects have been shown in both *in vitro* and *in vivo* studies to deliver therapeutic antibodies that retained biological activity after delivery into the skin[45].

Additionally, antimetabolites currently used as injectable therapy for periocular scars would be good candidates for AFR assisted topical delivery. Intralesional corticosteroids such as TAC have been used to treat pathological scars since the 1960s. They are thought to disrupt inflammatory cell migration, reduce the nutrient supply to scar tissue through vasoconstriction, and interfere with the metabolic processes of fibroblasts[46]. Typical treatment regimens entail injecting a 10 to 40 mg/mL concentration at 3 to 6 wk intervals for several months or until scar improvement is noted[8,47]. Most studies report significantly improved pliability and scar volume in 50% to 100% of enrolled patients[9,48,49]. Nevertheless, recurrence rates are relatively high, ranging from 9% to 50%, and side effects include hypopigmentation, skin and subcutaneous fat atrophy, telangiectasia, necrosis, and delayed wound healing[8,46].

5-fluorouracil (5-FU) is a pyrimidine nucleotide analogue first injected off-label for scar therapy by Manuskiatti *et al*[48] in 1989[50-52]. It competitively inhibits thymidylate synthase, disrupting DNA synthesis and blocking collagen formation[8,53]. Concentrations of 40 to 50 mg/mL are typically injected at intervals similar to those for intralesional steroids, although some authors use formulations as dilute as 1.4 to 3.5 mg/mL[9,54]. Haurani *et al*[53] reported a 50% reduction in scar volume, still maintained 1 year after the termination of therapy. Fourteen percent of patients had no significant response[53]. 5-FU has a more favorable side-effect profile, with relatively low rates of local erythema, ulceration and transient hyperpigmentation[8,46]. Hematologic derangements, pregnancy, bone marrow suppression and infection are generally considered contraindications, although significant sequelae have not been reported from local injection for scar therapy[8,9,51].

Combining intralesional TAC and 5-FU was superior to either alone in a prospective, double blinded trial[47]. Wang *et al*[46] reported 62.5% efficacy for hypertrophic scar monotherapy and 92% efficacy with combination therapy. TAC is generally mixed with 5-FU in a ratio ranging from 1:3 to 1:9[9,55]. Steroids appear to reduce the inflammation caused by injection of 5-FU, minimizing pain and swelling, and the decreased concentration of TAC significantly reduces the risk of atrophy and hypopigmentation[47].

CONCLUSION

Interest in new treatment options for the functional and cosmetic sequelae of periocular scars, particularly those causing cicatricial ectropion, has been growing rapidly among ophthalmologists and oculoplastic surgeons. In addition to traditional medical management and surgical repair, ophthalmologists have drawn ideas from the dermatology literature for the treatment of scars, particularly

keloids and hypertrophic scars. This has led to the application of topical agents, injectable metabolites, and the use of ablative and nonablative lasers in the treatment of periocular scar tissue and cicatricial ectropion. Although the combination of therapeutic agents with laser treatments is in its infancy, it is a promising treatment modality for periocular scar tissue.

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MINIREVIEWS

Review of laser and light therapy in the treatment of oculofacial pathology

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Abstract

Demand for non-invasive techniques to treat oculofacial pathology has allowed for the growth and development of several new laser and light therapy modalities. These modalities include the use of intense pulsed light (IPL) and photodynamic therapy (PDT), light-emitting diode devices, as well as ablative and non-ablative lasers. Therapeutic applications in the periorbital area may involve the treatment of vascular lesions, telangiectasias, dyspigmentation, photodamage, hypertrichosis, rhytids, and scars. Laser and light-based technology offers patients treatment options that range from conservative to aggressive, allowing for choices between subtle results with little downtime or dramatic results with longer downtime. Advantages of laser treatments, as compared to traditional medical and surgical treatments, include a longer lasting effect than some of the conservative therapies and the ability to serve as a happy medium between non-invasive topical medicine and invasive surgical techniques. For patients seeking non-invasive alternatives, these modalities confer a major advantage over incisional surgery. Understanding appropriate usage, side effects, and outcomes is before treating functional and cosmetic issues. Here we present a review of current treatment modalities, their use, side effects, and outcomes.

Key words: Intense pulsed light; Ablative lasers; Non-ablative lasers; Fractional lasers; Photodynamic therapy; Non-invasive techniques

Core tip: Laser and light treatments have become an essential addition in the oculoplastic service armamentarium for the management of different pathological oculofacial conditions as well as for aesthetic improvement. Both the unique anatomy of the periocular area, and one's individual treatment goals for the patient, must help tailor the choice of laser, the energy level used, and the depth of treatment to achieve an optimum result.

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INTRODUCTION

The demand for non-surgical treatment options for cosmetic and functional periorbital pathology has grown in recent years. Injectable soft tissue fillers[1] and neurotoxins[2] have maintained their popularity, as they are useful for addressing resting and dynamic rhytids as well as volume deficits. However, they are unable to address problems with the skin surface or quality. Chemical facial

Table 1 Light and laser applications

Type of laser/light	Specific type	Tissue target chromophore	Applications	Advantages	Disadvantages
IPL		Hemoglobin, melanin	Telangiectasias, pigmented lesions, hair removal, skin resurfacing	Not invasive/not a laser/light based	Not an option for darker skin types
PDT			Fine wrinkles, telangiectasias, hyper pigmentation	Treatment of specific areas, no damage to surrounding tissues	Pain during treatment
Ablative	CO_2	Water	Skin resurfacing, scars, lesions	Excellent results, especially in skin resurfacing	Prolonged postoperative period, increased risk for side effects (erythema, dyspigmentation)
	Er:YAG	Water	Wrinkles		
	Diode	Melanin	Hair removal, resurfacing		
Non ablative	QS Nd:YAG	Melanin	Tattoo removal, pigment lesions	Less aggressive, low risk for side effects	Less effective when compared to ablative lasers
	QS alexandrite	Melanin	Tattoo removal, pigment lesions		
	QS ruby	Melanin	Tattoo removal, pigment lesions		
	QS frequency-doubled Nd:YAG	Melanin, hemoglobin	Pigmented lesions, red tattoos		
	Pulsed dye (green)	Melanin, hemoglobin	Pigmented lesions, red tattoos, hemangiomas		
	Argon	Melanin, hemoglobin	Telangiectasias, PWS		
Fractionated	Ablative	Water	Dyspigmentation, acne, traumatic scarring, rhytides, skin resurfacing	Quick recovery	Erythema, edema, hyper-hypo-pigmentation, herpes simplex viral reactivation, bacterial infection
	Non ablative	Melanin, hemoglobin	Melasma, acne scars, hair removal, skin resurfacing		

IPL: Intense pulsed light; PDT: Photodynamic therapy; Er:YAG: Erbium-yttrium-aluminum-garnet; Nd:YAG: Neodymium-yttrium-aluminum-garnet.

peels, which vary in strength from mild alpha-hydroxy acids to intense phenol-based solutions, are an option to tighten and resurface the skin[3]. The mild peels, however, may not provide long-lasting, dramatic effects[4] and the stronger peels can not be used to treat darker skin types, can be painful, and are restricted in certain patients with cardiac conditions[5].

A multitude of laser and light-based technologies have been introduced to meet a broader range of needs. Concerns regarding excess upper or lower eyelid skin, periorbital rhytids, poor skin texture or pigmentation, presence of vascular lesions, or presence of scars may all be addressed by these modalities[6]. Current therapeutic options include light-based devices such as Intense Pulsed Light (IPL) Therapy[7], photodynamic therapy (PDT)[7], and light-emitting diode devices[7]. Laser alternatives include non-ablative[8] and ablative devices[8], both of which have the option of fractionated delivery. A newer modality that is outside the scope of this review utilizes radiofrequency energy for skin tightening and rejuvenation[6]. Each of these laser and light-based technologies are discussed below.

LIGHT AND LASER APPLICATIONS

All applications are summarized in Table 1.

IPL

IPL therapy is a non-invasive light-based technique that utilizes light in the wavelength range of 500 nm to 1200 nm to target the chromophores hemoglobin and melanin[9]. IPL has been successfully utilized to treat vascular and pigmented lesions of the oculofacial area[9], and may be used for hair removal[10] and photorejuvenation[11] as well. It is currently an FDA approved therapy for the treatment of photoaging. There is thought that IPL may be successful in reducing symptoms and improving clinical stigmata of dry eye syndrome associated with meibomian gland dysfunction in patients with facial rosacea[12]. The exact mechanism of action is unknown, but theories include obliteration of vessels leading to eyelid inflammation and/or heating of the meibomian glands, allowing for easier expression of the meibum.

IPL is administered by a flash lamp device that has the ability to emit light of multiple wavelengths. Individual filters are chosen to target preferential absorption by blood vessels or pigment, depending on the pathology requiring treatment. Unlike lasers, IPL uses a non-collimated, non-coherent light source. Moreno Arias *et al*[9] have proven that the use of different filters allows one to target red pigment for treatment of vascular lesions such as spider angiomas or telangiectasias, or melanin for

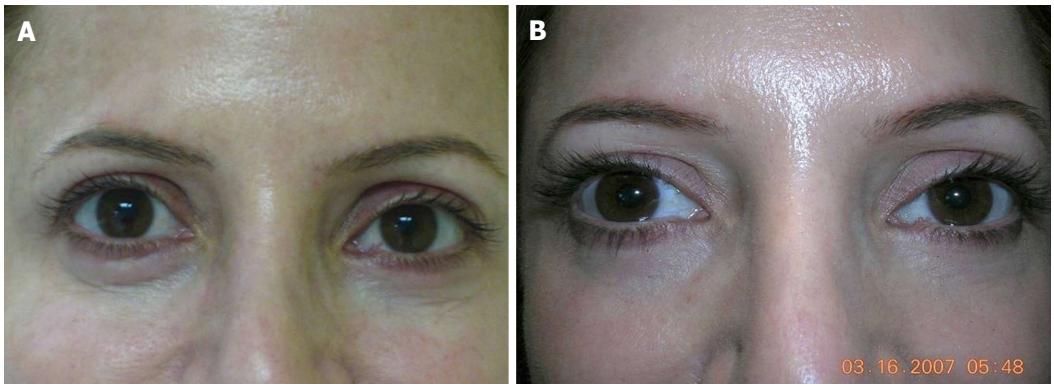

Figure 1 (A) pre and (B) post pre ablative laser treatment comparison shows improvement with reduction of the appearance of fine wrinkles, and improvement of the tone of the skin.

treatment of pigmented lesions such as actinic changes or freckles. Goldberg *et al*[11] have shown that IPL for photorejuvenation spares the epidermis and targets the dermis, generating collagen, and enabling skin tightening and contraction. Zandi *et al*[10] investigated the use of IPL for hair removal and proved that it is limited to pigmented follicles, as the target chromophore is melanin. The target chromophores for IPL also restrict its use primarily to patients of lighter skin types. Because the light is absorbed into pigment in the skin, patients with Fitzpatrick skin types V or VI are not good candidates for IPL use, and patients with skin type IV may require placement of a test spot before IPL treatment is considered[13]. Erythema of the treated areas is common for several days but is self-limited. Sun protection is required for all patients pre- and post-treatment. Uncommon side effects include pain, hypo- or hyper-pigmentation, and superficial crust or vesicle formation[14].

PDT

PDT was first used to target malignant cells by light activation of a photosensitizing agent [5-aminolevulinic acid (ALA) and ALA methyl ester (Me-ALA)] in the presence of oxygen[15]. PDT is commonly used to treat premalignant and malignant lesions such as actinic keratoses, Bowen's disease, superficial basal cell carcinoma, and other non-melanotic skin cancers. PDT has proved useful in the treatment of other inflammatory conditions, such as acne vulgaris and psoriasis, infectious lesions, such as dermatophytosis, onychomycosis, leishmaniasis, warts and molluscum contagiosum, and in benign conditions such as sebaceous hyperplasia and nevi. Recently, MacCormack[16] has proved that PDT is useful for the cosmetic treatment of fine wrinkles, telangiectasias and hyper pigmentation. One of the main advantages of PDT therapy is that it treats specific areas without damaging the surrounding tissues. Contraindications are rare, and limited to some specific photodermatoses as well as allergies to ALA and Me-ALA. Pigmented lesions are not indicated for PDT, as melanin is a fluorescence quencher and may also inhibit light penetration[16].

The most common adverse events include pain and a burning sensation limited to the term of the irradiation and several hours afterwards. Other adverse effects include photosensitivity, related to the duration of ALA or Me-ALA application and skin necrosis with consecutive scarring and hypo- and hyper-pigmentation[16].

ABLATIVE LASERS

As the desire to obtain cosmetic perfection grew, physicians began to search for other non-invasive approaches in the treatment of oculofacial pathology. In the early 1980s, ablative lasers were used more readily in the treatment of photoaging and scarring. To avoid many adverse reactions found in the first lasers, several short-pulsed, high-peak powered lasers were developed including the CW CO_2 laser and the erbium-yttrium-aluminum-garnet (Er:YAG) laser. These new lasers are better in their ability to control the depth of thermal damage at a specific pulse duration providing more accurate control and less overall damage as Alster[17] has demonstrated. The CO_2 laser, which has a higher ablation threshold and therefore targets the deeper tissues, is the most important surgical laser for cutting, vaporizing, and carbonizing. It emits a 10600-nm wavelength and is strongly absorbed by tissue water. Alexiades-Armenakas *et al*[18] in a review study have concluded that this laser is unique in that its penetration depth does not depend on melanin or hemoglobin. The CO_2 laser has proved useful in skin resurfacing and rejuvenation and even in blepharoplasty (Figure 1). This laser can also be beneficial in the improvement of fine wrinkles around the eyes. In general, this ablative laser is safer for skin types I -Ⅲ.

The Er-YAG laser, emits a wavelength of 2940 nm in the infrared range, closer to the absorption peak of water allowing for less thermal damage and quicker recovery time[19].

Ablative lasers have proved very useful in the treatment of facial rhytids, especially in the periorbital area which may not be improved with surgical face lift procedures. Scars from acne, trauma, and surgery are highly amenable to ablative laser techinques as well[18].

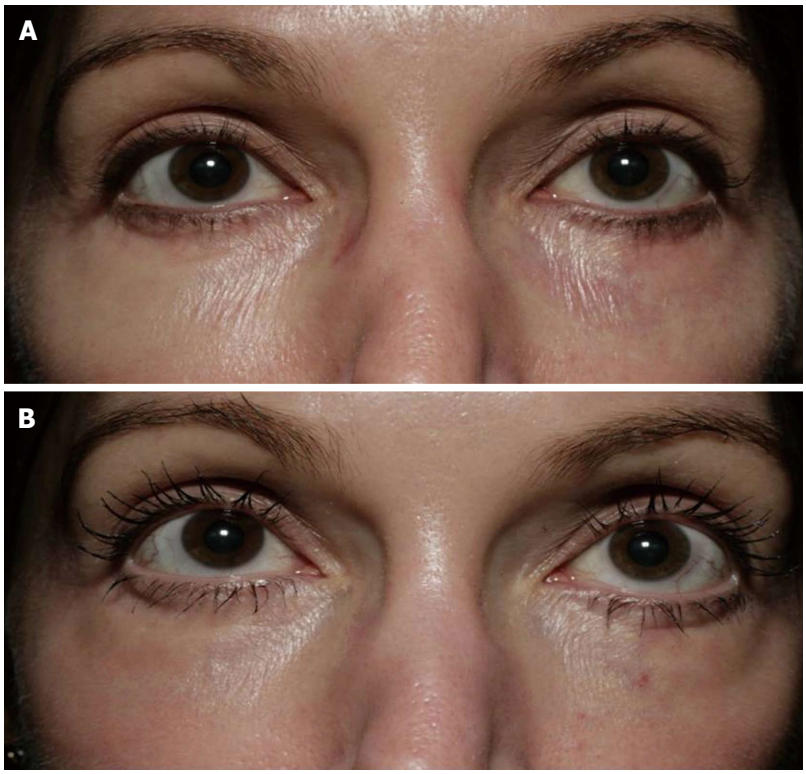

Figure 2 Visible light lasers. A: Patient demonstrating fine wrinkles prior to non ablative treatment of the upper and lower lids; B: Two weeks after a single treatment, the lids appear smoother with a subsequent reduction in wrinkles.

Absolute contraindications for laser treatment include active acne, deep acne pits or picks, and isotretinoin (Accutane) use in the past 2 years. Similarly, patients with reduced adnexal structures (*e.g.*, scleroderma, irradiation or burns) are poor candidates. History of herpetic infection is a relative contraindication only because most patients do not know their true status. Diseases with koebnerizing features, such as psoriasis or vitiligo, are also considered relative contraindications. Smokers are not excluded as treatment candidates[18].

Side effects following the ablative lasers include erythema, dyspigmentation (occurring more commonly in Fitzpatrick's skin types Ⅲ and Ⅳ), follicular, infectious, and eczematous reactions[18].

NON-ABLATIVE LASERS

Ablative lasers, although more effective, are also more aggressive and come with the potential for more side effects and longer recovery periods. This led to the development and introduction of newer, non-ablative systems. As with ablative lasers, non-ablative lasers have water as their chromophore and utilize wavelengths in the infrared range[8]. However, at these lower wavelengths water is only moderately absorbed, leading to slower heating and coagulation of the target tissue[20]. The primary goal is to stimulate collagen production and remodeling with little to no healing time. There are a number of non-ablative lasers currently available, including the neodymium-yttrium-aluminum-garnet (Nd:YAG)[21,22] and erbium glass (Er:Glass)[23] lasers in wavelengths of 1410 to 1550 nm. Visible light lasers such as the pulsed dye and pulsed 532 nm systems[24,25] (Figure 2), Q-switched Nd:YAG[26], and Q-switched alexandrite lasers also conservatively remodel with minimal downtime. They target pigment, including both endogenous melanin as well as tattoo ink, so are particularly effective at tattoo removal.

Ciocon *et al*[20] investigated non-ablative lasers, concluding that their biggest advantage is that they minimize the risks of temporary and permanent scarring by delivering dermal energy with concomitant surface cooling while leaving the epidermis intact. The wavelengths of these lasers have lower absorption coefficients than either the CO_2 or Er:YAG lasers, so a large volume of tissue can be heated without direct thermal conduction or damage. Scarring and texture change, although rare, are still risks during application[8].

Non-ablative lasers are less aggressive but adverse events such as erythema, edema, pain, burning and abnormal sensation of the eyelids may be present in the immediate postoperative period[20].

FRACTIONATED LASER DEVICES

Fractionated lasers, which are adaptations of ablative and non-ablative lasers, are designed to improve skin texture with minimal recovery time. Fractional photothermolysis was first introduced by Manstein *et al*[27] in 2004 as a modification of non-ablative laser therapy. This technology creates microscopic thermal zones of less than 400 μm diameter, extending to a depth of 1 mm or more. In between each treatment zone, the intervening tissue remains untouched. This allows for faster healing as the untreated tissue serves as a reservoir of healthy cells than migrate into the treatment zones. The treatment effect can be varied by changing the wavelength and pulse en-

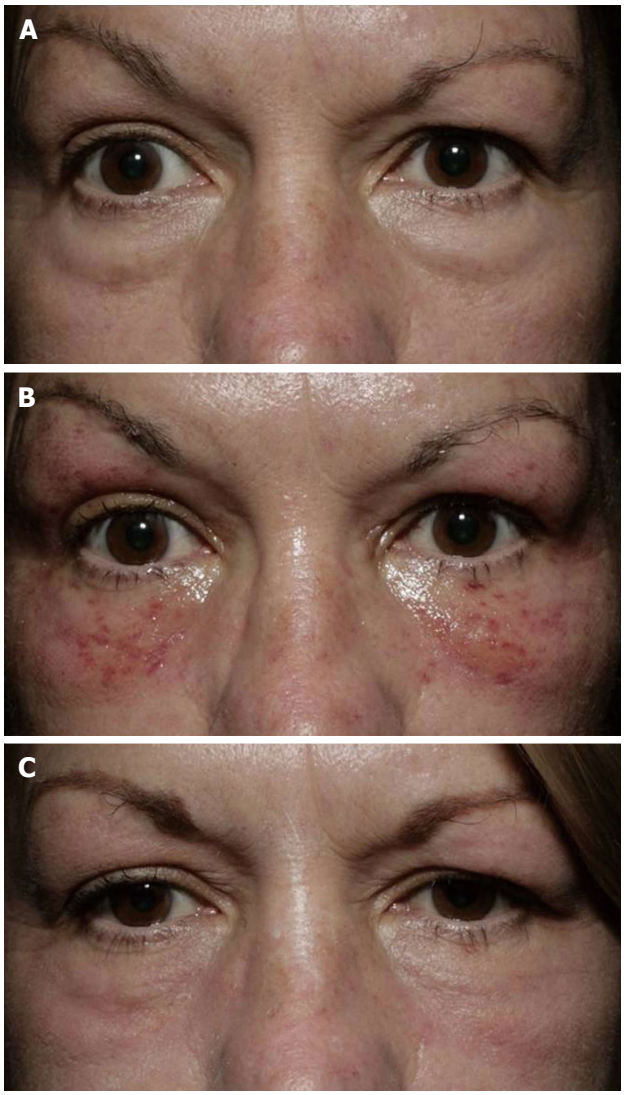

Figure 3 These lasers are useful for improvement of skin texture, dyspigmentation, acne or traumatic scarring, and rhytides around the eyes and mouth. A: Preoperative image before ablative fractional treatment of upper and lower lids; B: Three days post treatment, erythema and edema are present, skin is not completely re-epithelialized; C: One week post treatment a reddish hue to the skin is still visible.

ergy of the device[28]. In 2007, ablative fractional resurfacing devices were introduced, including fractional CO_2 and fractional 2940 nm Er:YAG lasers[29,30]. Both types of lasers induce collagenesis and epidermal turnover within several days. Since water is the target chromophore, collagen, blood vessels, and keratinocytes are all treatable. These lasers are useful for a wide array of indications including improvement of skin texture, dyspigmentation, acne or traumatic scarring, and rhytides around the eyes and mouth[27,31,32] (Figure 3). Dermal targeting allows for wrinkle effacement, scar revision and skin tightening. Targeting wider epidermal areas using ablative fractional lasers allows for treatment of photoaging changes including solar lentiges and dyspigmentation[33]. More limited data support the possible use of non-ablative fractional resurfacing for striae distensae[34-36], melasma[37-40], Nevus of Ota[33], poikiloderma of Civatte[41], and minocycline-induced hyperpigmentation[42].

In the immediate postoperative period, patients may report erythema, edema, flaking, xerosis, pruritis, bronzing, and acneiform eruptions[32]. Downtime is minimal for non-ablative devices, and may range from 1-7 d for ablative devices, during which desquamation may last for several days[32]. Rare side effects include hyper- and hypopigmentation, herpes simplex viral reactivation, and bacterial infection. Particular concern for scarring and hypopigmentation increases with higher energy fluences and more aggressive treatment, although the risks are significantly lower than those seen in fully ablative laser therapy.

LASER COMPLICATIONS AND MANAGEMENT

Although lasers target specific chromophores, the surrounding scatter and the resulting thermal effect could cause collateral damage[43]. While the main tissue chromophores are targeted, other adjacent structures that are also rich in these chromophores are susceptible to inadvertent damage.

Laser complications can range from mild eyelid swelling and erythema, skin infections, hypo and hyper pigmentation to accidental corneal injury and potentially blinding macular injury[44,45].

Laser and light injury can be prevented if certain guidelines are followed such as eye protection during treatment for the patient, the operator, the observer and the assistant. Also, laser warning signs must be placed at the entrance of the laser treatment room when lasers are operating; adequate laser safety training for personnel must be provided. Potential injury to the surrounding tissues can be minimized by adjusting the treatment parameters appropriately, using cooling devices during the procedure, applying ice packs after the procedure, and elevating the head of the bed[46].

CONCLUSION

The introduction of laser and light-based treatment has given ophthalmologists a powerful tool to manage periocular pathology and address cosmetic concerns. They offer multiple treatment options to patients seeking non-surgical oculofacial rejuvenation, and are best utilized as one component in an overall treatment strategy that may also include injectable neurotoxins, soft tissue fillers, or facial peels. Patients must be counseled regarding the limitations of these modalities, and must have realistic expectations of the outcomes. Use of this technology can provide long-lasting results, and in some cases can provide a very good alternative to surgical intervention.

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RETROSPECTIVE STUDY

Presenting clinical features of patients with vitreoretinal lymphoma

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Abstract

AIM: To assess the presenting clinical features, time from presentation to diagnosis and association with central nervous system (CNS) lymphoma in patients with vitreoretinal lymphoma.

METHODS: Retrospective case series of patients diagnosed with vitreoretinal lymphoma between 2009 and 2011 at a single center.

RESULTS: Fifteen eyes in 9 patients were included. Common presenting ocular symptoms included blurred vision (78%) and worsening floaters (44%) with an average symptom duration prior to presentation of 88.4 d (range 7-365 d). Common ophthalmic exam findings were vitreous haze (89%) and subretinal lesions (56%). The average time from presentation to diagnosis was 56.3 d (range 16-180 d). All patients were diagnosed with large B-cell lymphoma according to pathology results. Lymphoma was restricted to the eye in 33%, while 67% of patients had CNS involvement. Of the patients with secondary vitreoretinal lymphoma, 67% initially presented with CNS lymphoma while 33% initially presented with vitreoretinal lymphoma. Of the patients with CNS involvement, memory loss (67%) was the most common presenting symptom.

CONCLUSION: Vitreoretinal lymphoma most commonly presents with symptoms of blurred vision and/or worsening floaters and vitreous haze on exam. The average time from presentation to diagnosis may be decreasing with increased awareness among clinicians.

Key words: Primary vitreoretinal lymphoma; Secondary vitreoretinal lymphoma; Primary central nervous system lymphoma; Primary intraocular lymphoma

Core tip: Vitreoretinal lymphoma is a rare, highly malignant lymphoma that can present a diagnostic challenge to clinicians. This case series was designed to identify presenting clinical features associated with vitreoretinal lymphoma.

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INTRODUCTION

Vitreoretinal lymphoma is a rare, highly malignant non-Hodgkin lymphoma, usually of B-cell origin[1]. It more commonly affects the elderly, with a reported mean age

Table 1 Demographic and clinical features of patients with vitreoretinal lymphoma

Patient No.	Age/gender	Bilateral involvement (Y/N)	Presenting ocular symptoms	Symptom onset (days prior to presentation)	Presenting visual acuity	Exam findings	Time from presentation to diagnosis (d)
1	83 yr/F	N	Cloudy vision	30	20/20	Vitreous cells	120
2	65 yr/F	Y	Worsening floaters and blurred vision	120	20/60	Vitreous cells	17
3	86 yr/F	Y	Worsening floaters and blurred vision	365	CF 1′	Vitreous haze and subretinal lesions	45
4	68 yr/M	Y	Blurred vision	Unable to determine	20/60	Vitreous cells and subretinal lesions	30
5	70 yr/F	Y	Cloudy vision	60	20/40	Vitreous cells	16
6	67 yr/M	N	Worsening floaters and blurred vision	7	20/100	Subretinal lesion	180
7	81 yr/M	Y	Blurred vision	14	20/80	Vitreous cells/ haze	30
8	58 yr/M	Y	Worsening floaters and blurred vision	21	20/150	Vitreous haze and subretinal lesions	45
9	63 yr/M	N	Blurred vision	90	20/400	Vitreous cells and subretinal lesions	24

F/M: Female/Male; Y/N: Yes/No; CF 1′: Counting fingers at 1 foot.

of 50-70[1] and is commonly considered to be a localized presentation of primary central nervous system lymphoma[2]. Delays in diagnosis are common given its morphologic similarity to vitreous inflammation. There are limited published series reporting the presenting clinical features of vitreoretinal lymphoma[3-7]. The purpose of this study is to assess the presenting clinical features including initial symptoms, symptom duration, visual acuity, exam findings, and time from presentation to diagnosis in patients diagnosed with vitreoretinal lymphoma.

MATERIALS AND METHODS

Approval for this single-center retrospective case series was obtained from the Institutional Review Board at Oregon Health and Sciences University. Patients were identified through pathology records between January 2009 and December 2011 at the Casey Eye Institute, Oregon Health and Science University. Inclusion criteria were a diagnosis of vitreoretinal lymphoma by vitreous aspirate or diagnostic vitrectomy. Nine patients met the inclusion criteria. The medical records of all 9 patients were extensively reviewed from January 2009 through May 2012.

Patient demographics including gender and age at diagnosis were assessed. Outcome measures assessed included presenting ocular symptoms, symptom duration, presenting visual acuity, ophthalmological exam findings, bilateral involvement at presentation, time from presentation to diagnosis, association with central nervous system (CNS) lymphoma and presenting CNS symptoms.

RESULTS

Fifteen eyes in 9 patients diagnosed with vitreoretinal lymphoma by vitreous aspirate or diagnostic vitrectomy were included. The median observation period was 18 mo (range 4-28 mo). Demographic and clinical features of the patients are summarized in Table 1. Of the 9 patients, 5 were male and 4 were female. The median age at diagnosis was 68 years (range 58-86 years). Presenting ocular symptoms included blurred vision in 7 patients (78%), worsening floaters in 4 patients (44%), and cloudy vision in 2 patients (22%). All 4 of the patients with worsening floaters also reported blurred vision. The median symptom duration prior to presentation was 45 d (range 7-365 d). Best corrected visual acuity at presentation ranged widely among the cohort. One patient (11%) presented with no visual impairment (visual acuity of 20/20). Three patients (33%) had mild visual impairment with a visual acuity of 20/30 to 20/60, 3 patients (33%) had moderate visual impairment with a visual acuity of 20/70 to 20/160 and 2 patients (22%) had severe visual impairment with a visual acuity of 20/200 or worse. Ophthalmic exam findings included vitreous cells/haze in 8 patients (89%) and subretinal lesions in 5 patients (56%). Four patients (44%) had vitreous haze and subretinal lesions on exam. Exam findings were bilateral at presentation in 6 patients (67%). The median time from presentation to diagnosis was 30 d (range 16-180 d).

Association with CNS lymphoma

All patients were diagnosed with large B-cell lymphoma according to pathology results. Of 9 patients, 4 patients (44%) had a history of CNS lymphoma and developed secondary vitreoretinal lymphoma. All 4 patients were treated for CNS lymphoma with one patient receiving whole brain radiation, 3 patients receiving chemotherapy, and one patient undergoing surgery. Of the 3 patients receiving chemotherapy, 2 were treated with methotrexate. At the time of vitreoretinal lymphoma diagnosis, 3 of the 4 patients were free of CNS disease. The time from CNS lymphoma remission to diagnosis of vitreoretinal lymphoma ranged from 9-36 mo. Two patients (22%) developed CNS lymphoma subsequent to the diagnosis of primary vitreoretinal lymphoma (PVRL). One patient was treated with intravitreal methotrexate and rituximab while

the other patient deferred treatment. The time from diagnosis of PVRL to diagnosis of CNS disease ranged from 3-7 mo. Three patients (33%) had PVRL without CNS involvement at the end of the study period with duration of follow-up after diagnosis of PVRL ranging from 8-29 mo. Of 6 patients with CNS lymphoma, presenting CNS symptoms included memory loss in 4 patients (67%), speech problems in 2 patients (33%), difficulty walking in 1 patient (17%), and generalized seizure in 1 patient (17%). All 6 patients were diagnosed with CNS lymphoma by magnetic resonance imaging.

DISCUSSION

Vitreoretinal lymphoma is a rare, highly malignant lymphoma that can present a diagnostic challenge to clinicians. This case series was designed to identify presenting clinical features associated with vitreoretinal lymphoma. In our cohort of 9 patients, the median age at diagnosis of vitreoretinal lymphoma was 68 years with all patients > 50 years of age at diagnosis. This is consistent with previous reports that vitreoretinal lymphoma most commonly affects the elderly[1,3-7]. 56% of patients in our cohort were male. Some previous studies have suggested a female predominance[1,3-5] while others have not[6,7]. The percentage of patients with bilateral involvement at presentation was 67%, which is within the previously reported range of 60%-90%[1,3]. The most common presenting ocular symptom was blurred vision in 7 patients (78%). Additionally, vitreous cells/haze was the most common ophthalmic finding, present in 8 patients (89%). These findings are also consistent with prior published case series[3-7]. Best corrected visual acuity at presentation was highly variable in our cohort, ranging from no visual impairment (visual acuity of 20/20) to severe visual impairment (visual acuity of 20/200 or worse). Wide variation in presenting visual acuities has been reported in a large series by Frenkel *et al*[8].

In the past, delays in the diagnosis of vitreoretinal lymphoma have been common due to its slow onset and ability to imitate other conditions. Most recently, Akpek *et al*[9] reported that the diagnosis can be achieved within 12 mo in 80% of patients. In our series, the median time from presentation to an eye care provider to diagnosis of vitreoretinal lymphoma was 30 d (range 16-180 d). This may indicate an increased awareness by clinicians of the disease. Additionally, in our cohort, 4 of the 9 patients (44%) had a history of CNS lymphoma prior to development of secondary vitreoretinal lymphoma, potentially leading clinicians to suspect the diagnosis earlier in these patients given the known association. However, among the 5 patients who presented with PVRL and no history of CNS lymphoma, the median time from presentation to diagnosis only slightly increased to 45 d (range 30-180 d). Two of the 5 patients (40%) with PVRL subsequently developed CNS involvement during our study period. According to Coupland *et al*[1], 65%-90% of patients presenting with PVRL will go on to develop CNS involvement. Our percentage may be lower given the brief duration of our study period. It is possible that our patients diagnosed with PVRL will develop CNS involvement in the future.

Our study has several limitations, including the retrospective nature of the data, the small number of patients and the brief study period. We chose to limit our study period to the prior 3.5 years (January 2009-May 2012) because we had comprehensive medical records of all patients during this time period. In the future, it will be interesting to evaluate treatment response, visual outcomes and survival rates over a longer time period in similar cohorts of patients.

In conclusion, vitreoretinal lymphoma most commonly presents with symptoms of blurred vision and/or worsening floaters and vitreous haze on exam. Visual acuity is highly variable in the presentation of PVRL. The average time from presentation to diagnosis may be decreasing with increased awareness among clinicians.

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COMMENTS

Background

Vitreoretinal lymphoma is a rare, highly malignant lymphoma. It can present a diagnostic challenge to clinicians, given its morphologic similarity to vitreous inflammation. It can develop primarily in the eye or develop in association with central nervous system (CNS) lymphoma.

Research frontiers

There are limited published series reporting the presenting clinical features of vitreoretinal lymphoma. Given the diagnostic challenges associated with vitreoretinal lymphoma, it is important to further distinguish its' presenting features to aid in timely diagnosis.

Innovations and breakthroughs

Recent reports have shown that the diagnosis can be achieved within 12 mo in 80% of patients. In this study, the average time from presentation to diagnosis was even less, suggesting increased awareness among clinicians.

Applications

By further understanding the presenting clinical features of vitreoretinal lymphoma, this study may help aid in more timely diagnosis, contributing to earlier treatment of patients with vitreoretinal lymphoma.

Terminology

Primary vitreoretinal lymphoma, formerly known as primary intraocular lymphoma, is the most common lymphoma affecting the eye, and may go on to affect the CNS. Secondary vitreoretinal lymphoma occurs when patients diagnosed with primary CNS lymphoma develop an ocular manifestation of their lymphoma.

Peer review

Paper is about primary and secondary vitreoretinal lymphoma. Generally well written and informative.

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