

Xanthelasma: An Update on Treatment Modalities

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Abstract

Xanthelasmas are localized accumulation of lipid deposits on the eyelids. Lesions are typically asymptomatic and treatment is often sought for cosmetic purposes. Unfortunately, there is paucity of strong evidence in the literature for the effective treatment of normolipidemic xanthelasmas. A literature search using the term "xanthelasma" was carried out in PubMed and Medline databases. Only articles related to treatment were considered and analyzed for their data. Commonly cited treatments include topical trichloroacetic acid, liquid nitrogen cryotherapy, and various lasers including carbon dioxide, Er:YAG, Q-switched Nd:YAG, and pulse dye laser. However, traditional surgical excision has also been used. This article reviews these currently accepted modalities of treatment.

Keywords: Normolipidemic xanthelasmas, xanthelasma, xanthelasma palpebrarum, xanthelasma treatment

INTRODUCTION

Xanthelasmas are yellowish papules and plaques caused by localized accumulation of lipid deposits commonly seen on the eyelids.

The prevalence is estimated at 4%,^[1] with an incidence of 1.1% in women and 0.3% in men.^[2] The age of onset can range from 15 to 73 years, although typical peaks are seen in the fourth and fifth decades. In around half of the cases, it can be associated with an underlying hyperlipidemia, and a presentation prior to the age of 40 should prompt screening to rule out underlying inherited disorders of lipoprotein metabolism.^[3]

Although the exact pathogenic mechanism is not fully understood, cutaneous xanthelasma represents the deposition of fibroproliferative connective tissue associated with lipid-laden histiocytes, also known as foam cells. Histologically, these foam cells are typically found in the middle and superficial layers of the dermis in perivascular and periadnexal locations, with associated fibrosis and inflammation.^[4]

Primary hyperlipidemia is caused by genetic defects in the receptors or enzymes involved in lipid metabolism. Inherited disorders of low-density lipoprotein (LDL) cholesterol metabolism are typical examples that are seen

in 75% of those with familial hypercholesterolemia.^[2] The pathogenesis in this cohort of patients is thought to be secondary to elevated serum lipoprotein levels, which leads to extravasation of the lipoprotein through dermal capillary blood vessels and subsequent macrophage engulfment.

Secondary causes of hyperlipidemia include certain physiological states and systemic diseases. Examples include pregnancy, obesity, diabetes mellitus, hypothyroidism, nephrotic syndrome, and cholestasis.^[5-8] Certain medications such as estrogens, tamoxifen, prednisolone, oral retinoids, cyclosporine, and protease inhibitors can also lead to a state of hyperlipidemia.^[9-11]

The most common cutaneous presentation is xanthelasma palpebrarum (XP).^[2] They present as soft symmetrical, bilateral, yellow, thin polygonal papules and plaques typically in the periorbital area. Other sites that may be affected include the neck, trunk, shoulders, and axillae.^[2] There is no association between xanthelasmas and high-density lipoprotein or triglyceride levels.

Christoffersen *et al.*^[12] found that independent of well-known cardiovascular risk factors, the presence of

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XP appeared to be a predictor of risk for myocardial infarction, ischemic heart disease, severe atherosclerosis, and death in the general population. Contrary to common belief, arcus senilis of the cornea is not an independent predictor of risk.^[12]

Persistent XP should be distinguished from a chalazion, sebaceous hyperplasia, syringoma, nodular basal cell carcinoma, and necrobiotic xanthogranuloma (NXG). NXGs, a form of non-Langerhans histiocytosis, are red-brown, violaceous, or yellowish cutaneous papules and nodules that evolve to form infiltrated plaques, commonly in the periorbital region. They are frequently associated with monoclonal gammopathy and other hematological malignancies.^[13]

XP is typically asymptomatic and treatment is often sought for cosmetic purposes. Unfortunately, there is paucity of strong evidence in the literature for the effective treatment of XP. A literature search using the term “xanthelasma” was carried out in PubMed and Medline databases. Only articles related to treatment were considered and analyzed.

TREATMENT

XP is a benign asymptomatic lesion, not associated with any cutaneous complications; however, treatment is often sought for cosmetic reasons.

There is limited evidence in the literature for the effective treatment of normolipidemic XP. Commonly cited treatments include topical trichloroacetic acid (TCA), laser ablation, and surgical excision. There are also case reports of XP responding to systemic interleukin-1 blockade and cyclosporine-A therapy.^[10,14] We have reviewed the most common treatment modalities used for normolipidemic XP, their associated efficacy, particular limitations, and side effects. This is summarized in Table 1.

SYSTEMIC THERAPY

ProbucoI

There are reports of successful treatment using oral probucoI in the literature. It is proposed that probucoI, an antioxidant, acts by potentially inhibiting atherogenesis through limiting the oxidative modification of LDL cholesterol essential for foam-cell formation.^[15] Miyagawa *et al.*^[16] reported a case, of diffuse normolipemic plane xanthoma including XP, who was successfully treated with probucoI. Harris *et al.*^[17] showed 68% of xanthelasma regressed after probucoI therapy.

Alirocumab

Alirocumab, a monoclonal antibody that belongs to a novel class of anticholesterol therapy through inhibition of Proprotein convertase subtilisin/kexin type 9 (PCSK9), is primarily used in the treatment of hypercholesterolemia.

Table 1: Treatment options available with the studies

Type of treatment	Type of study ^(Ref.)	Number of patients
ProbucoI	Case report ^[16]	1
Alirocumab	Case report ^[18]	1
TCA	Prospective study ^[19]	30
	Randomized trial ^[20]	51
	Case series ^[22]	24
	Pilot study ^[24]	15
	Comparative study ^[39]	21
	Case series ^[25]	4
Liquid nitrogen cryotherapy	Case series ^[26]	12
Pingyangmycin	Pilot study ^[27]	15
CO ₂ laser	Prospective study ^[19]	30
	Case series ^[30]	23
	Case series ^[31]	10
	Pilot study ^[24]	15
	Randomized comparative study ^[32]	20
	Comparative study ^[38]	58
Er:YAG laser	Case series ^[36]	30
	Case series ^[37]	15
	Comparative study ^[38]	58
	Comparative study ^[39]	21
	Comparative study ^[44]	40
Q-switched Nd:YAG laser	Case series ^[41]	37
Argon laser	Case series ^[42]	24
	Comparative study ^[44]	40
KTP laser	Case series ^[45]	14
Pulsed dye laser	Case series ^[46]	20
Diode laser	Case series ^[47]	16
Surgery	Comparative study ^[38]	58
	Retrospective review ^[48]	95

Civeira *et al.*^[18] reported rapid resolution of XP after treatment with alirocumab in a middle-age man, with severe high levels of LDL cholesterol due to a familiar hypercholesterolemia. The regression of the XP was associated with lowering of LDL cholesterol concentrations.^[18]

TOPICAL THERAPY

Chemical peel

TCA is a form of destructive therapy, used topically at concentrations of 50%–100%. The approach is relatively simple. It is applied in a circular manner, carefully ensuring the greatest amount of TCA is smeared at the margin of the lesion. The treatment area is then neutralized with sodium bicarbonate.

Mourad *et al.*^[19] reviewed the efficacy and tolerability of different concentrations of TCA in the treatment of patients with XP. TCA concentrations of 35%, 50%, and 70% were tested. The authors initially degreased the skin using cotton gauze soaked in acetone. Sensitive

areas, for example, the inner canthus and nasolabial folds, were protected with petrolatum ointment. TCA was then applied using a cotton-tipped applicator until solid frosting without pink background was achieved. This was usually seen within 30 s to 2 min. The area was then neutralized and rinsed with cold water followed by the application of a thin coat of antibiotic ointment and sunscreen.^[19]

TCA 70% was found to be the most effective concentration. It was well tolerated and associated with significant clinical efficacy. This concentration required the least number of sessions in the treatment of XP. Furthermore, it was noted that TCA 70% was particularly useful in treating papular lesions whereas TCA 50% was effective for macular xanthelasma. A study by Haque and Ramesh^[20] mirrored these findings. They also concluded that TCA 70% was effective in treating flat plaques; however, TCA 100% was required for papulonodular lesions.^[20]

Overall, TCA therapy for XP was found to be more effective for smaller lesions, with repeated procedures resulting in pigmentation and scarring.^[21] In general, postinflammatory hyper- and hypopigmentation with TCA is reported at a frequency of 9%–12.5% and 21.5%–33.4%, respectively.^[20,22] Some studies reported that this was dependent on the TCA concentration, whereas others did not corroborate this association.^[20,22,23] It is also important to note that if TCA is applied near the eyelid, there is a risk of scar formation and subsequent risk of ectropion development. Existing literature suggests recurrences ranging between 25% and 39%,^[20-22] with Goel *et al.*^[24] describing a recurrence rate of 34.5% at 6-month follow-up in their cohort.

Liquid nitrogen cryotherapy

Liquid nitrogen cryotherapy is a simple and effective treatment option. The risk of intense swelling due to the lax skin tissue in the eyelid is the reason this treatment is generally avoided in XP. However, Labandeira *et al.*^[25] published a case series of XP treated with very short freeze time. They reported clearance of lesions in all cases with only minor swelling associated and no recurrences during a 10-year period.^[25]

The proposed mechanism of action of cryotherapy is suggested to be associated with vasoconstriction and microthrombi formation caused by cryo-induced cell death. This leads to tissue ischemia and cell death. Potential adverse effects seen with cryotherapy include edema, vesicular formation, and blister formation depending on intensity of inflammatory response. These correlate with the length of freezing and thus the temperature that the tissue reaches.^[25]

Pingyangmycin

Wang *et al.*^[26] described the treatment of XP with intralesional pingyangmycin, a broad-spectrum antitumor antibiotic. A total of 12 patients with 21 lesions received 2

treatment sessions, and in all patients except 1, the result was satisfactory. One patient experienced local recurrence 12 months after treatment. The authors described no severe associated complications.

ENERGY-BASED DEVICES

Radio-frequency ablation

Dincer *et al.*^[27] evaluated the use of low-voltage radio-frequency (RF) ablation in the treatment of XP. Of the 15 patients who participated in the study, 9 achieved an improvement of greater than 75%. The authors concluded that this modality of treatment was effective in the treatment of XP, in particular lesions close to the eye and those that are multiple especially with indistinct borders.^[27]

A comparative study by Reddy *et al.*^[28] evaluated the efficacy of RF ablation versus TCA in the treatment of XP. Although both treatments resulted in similar improvement scores, RF ablation required fewer sessions to achieve more than 75% clearance of lesions. However, at 4 weeks posttreatment, 40% in the RF group and 15% in the TCA group had scarring, and 45% in the RF group and 30% in the TCA group had pigmentation.^[28] Although fewer treatment sessions were required with RF ablation to achieve an excellent result, the treatment was associated with more complications comparatively.

Laser ablation

Laser ablation has been used to deliver targeted therapy in the treatment of XP. The mechanism of action is proposed to include (1) destruction of perivascular foam cells via thermal energy damage and (2) coagulation of dermal vessels leading to blockage of further lipid leakage into tissue, thus preventing recurrence. The use of a variety of lasers has been described in the literature, including carbon dioxide (CO₂), argon, erbium (Er), and pulsed dye lasers. The CO₂, neodymium-doped yttrium argon garnet (Nd:YAG), Er:YAG, and 1450-nm diode lasers all use longer wavelength of light absorbed best by cellular water, thus allowing their use in removal of epidermal lesions.^[29] Argon and pulse dye lasers, on the other hand, use shorter wavelengths of light, preferentially absorbed by hemoglobin, and therefore are primarily used for vascular lesions.^[29]

CO₂ laser

CO₂ is considered the gold-standard ablative laser. The vaporization of water within cells results in the ablation of skin layer by layer.^[29] A number of studies using CO₂ laser to treat patients with XP have been reported. The overall outcome was excellent, and complete initial resolution was achieved in the majority of cases. Raulin *et al.*^[30] published a large case series of 23 patients receiving high-energy ultrapulsed CO₂ laser therapy. The ultrapulsed variation enables vaporization of a thin layer of tissue whereas the pulses allow time for thermal relaxation of surrounding

tissue.^[31] All lesions were successfully removed, with no scarring associated and a recurrence rate of 13% at 10 months. The authors recommended treatment should be performed in the early stages of XP development to prevent recurrence.

Esmat *et al.*^[32] compared the efficacy and safety of super-pulsed (SP) and fractional CO₂ laser treatment for XP in a prospective randomized study. Bilateral XP lesions in 20 patients were treated with either a single session of ablative SP CO₂ or 3–5 sessions of ablative fractional CO₂ at monthly intervals. Lesions treated with SP CO₂ laser showed significantly better improvements and patient satisfaction in comparison with fractional CO₂ laser; however, scarring and recurrence were also higher.^[32]

CO₂ laser therapy has also been compared to other treatment modalities. A comparison study using 30% TCA and CO₂ laser for the treatment of XP in 50 patients showed that both these modalities were effective treatments for clinically mild lesions.^[24] The laser group achieved complete clearance in all patients, in contrast to the TCA group who achieved a complete clearance rate of 56%. The CO₂ laser was the superior treatment option for severe lesions due to its associated coagulative effect that spreads beyond the ablative zone. Unfortunately, recurrence was a concern with both treatments, particularly for lesions that extend deep into the dermis. At 6 months, the recurrence rate with TCA was 34.8%, consistent with existing literature that reports rates ranging from 25% to 39%.^[20-22] The recurrence rate with CO₂ at 6 months, in this study, was 16%.^[24] The recurrence rates reported in the literature for CO₂ are variable from no recurrence after 4 years^[33] to 13% at 10 months.^[30]

The efficacy of CO₂ laser therapy has also been compared to higher concentrations of TCA. Mourad *et al.*^[19] found CO₂ laser ablation to be as effective as TCA 70% in the treatment of XP. Side effects reported include postinflammatory hyperpigmentation (22.2%) and hypopigmentation (33.3%).^[19,34]

Er:YAG laser

Er:YAG laser, a purely ablative laser, has a smaller thermal coagulation zone in comparison to CO₂ laser, a classic device for skin resurfacing. The latter is associated with higher risk of scarring. The Er:YAG also has the added advantage of faster healing time, shorter duration of postlaser erythema, and postinflammatory hypo- and hyperpigmentation.^[35]

Mannino *et al.*^[36] treated 30 patients with a total of 70 xanthelasma lesions using Er:YAG laser. All lesions were effectively removed with no associated scarring or dyschromia.^[36] The follow-up observation period was 12 months. Similar effective results (100% lesion removal) were also seen in a study conducted by Borelli and Kaudewitz^[37] who treated 33 xanthelasma lesions with Er:YAG laser.

Another study by Lieb *et al.*^[38] found that the wound healing was slower with CO₂ compared with Er:YAG laser due to its larger associated thermal necrosis zone. The latter form of laser also had excellent results in the treatment of superficial xanthelasma. However, the authors concluded that CO₂ laser was better suited for deeper lesions possibly due to its associated hemostatic property.^[38]

The efficacy and complication rates of Er:YAG laser ablation in comparison to 70% TCA in the treatment for XP have also been reviewed. Güngör *et al.*^[39] treated different XP lesions in the same patient using these two treatment modalities. They reported that both treatments have similar effectiveness and complications rates.

Q-switched Nd:YAG laser

The benefits using the 1064-nm Q-switched Nd:YAG laser are not clear. Fusade^[40] reported a case series of 11 patients with a total of 38 xanthelasma lesions. After a single course of treatment, they noted an excellent response (greater than 75% clearance) in six patients, a good response (51%–75% clearance) in a further two patients, and moderate (25%–50% clearance) response in the remainder.^[40] However, it is important to note none of the patients achieved complete clearance.

Furthermore, these promising findings could not be replicated by Karsai *et al.*^[41] who treated a total of 76 lesions in 37 patients with 2 sessions of Q-switched Nd:YAG laser (1064-nm and 532-nm wavelengths). Fifty-seven lesions were treated with the 1064-nm wavelength and 19 with the 532-nm wavelength. The overwhelming majority of patients showed no clearance.^[41] The early disappointing results accounted for the high dropout rate; therefore, the authors advised against using Q-switched Nd:YAG laser treatment for XP due to poor clearance.^[41]

Argon laser

Argon laser coagulation of xanthelasma lesions represents an alternative laser treatment. Basar *et al.*^[42] treated 40 eyelids of 24 patients with XP using argon green laser. They reported that all lesions responded to therapy with a good cosmetic outcome in 85% of cases. The treatment was well tolerated with no associated complications or functionally relevant scar development.^[42] Blue-green argon laser was used by Ruban *et al.*^[43] to treat 25 patients with a total of 101 xanthelasmas. This resulted in a good cosmetic outcome in 83% of patients. Minimal scarring and slight dyschromia were seen in 13.3%, and visible scarring and marked dyschromia were evident in 3.3% of patients.^[43]

The effectiveness of Er:YAG and argon lasers in the treatment of xanthelasma has also been evaluated. Abdelkader and Alashry^[44] treated 40 xanthelasma lesions with argon laser and reported an excellent result in approximately 72% of cases. Small lesions less than 1 cm^[2] responded very well regardless of their firmness, whereas large lesions required more than one treatment session

given at 2 weeks apart. However, the major disadvantage reported with argon laser photocoagulation is significant recurrence rate at 50% within the first 12–16 months after treatment,^[35] with the majority occurring at the margin. Therefore, Abdelkader and Alashry^[44] recommended treating the margin of the xanthelasma well, which may explain the no recurrence seen at 6 months in their study.

Potassium titanyl phosphate laser

Potassium titanyl phosphate (KTP) laser works on the principle of selective photothermolysis. One study used KTP laser (532 nm) to treat xanthelasma in 14 patients and reported an efficacy of 85.7% without side effects.^[45]

Pulsed dye laser

Karsai *et al.*^[46] described the use of 585-nm pulsed dye laser in 20 patients with XP. A total of 38 lesions were treated. The authors described promising results with majority of the patients achieving greater than 50% clearance rates.^[46] Reported side effects included purpura, edema, and postinflammatory hyperpigmentation.

Diode laser

Although the 1450-nm diode laser is no longer used, the principle behind its use in the treatment of XP stemmed from data showing photothermal destruction of sebaceous glands in the mid-dermis. Park *et al.*^[47] treated XP with 1450-nm diode laser and a cryogen cooling spray. They showed 40%–80% clearance in the majority of patients and reported minimal side effects of mild, transient postinflammatory hyperpigmentation and localized edema lasting 3–4 days.^[47]

SURGERY

Traditionally, surgical excision has been used and often yields excellent cosmetic outcomes. Various surgical techniques have been advocated.

The classic blepharoplasty may be used to excise the xanthelasma in a serial staged approach, whereas Le Roux's technique involves a modified blepharoplasty approach.^[48] Recurrence, however, is common, and reported to be up to 40% and 60% following primary and secondary excision, respectively.^[48]

Lee *et al.*^[48] conducted a 4-year retrospective review of patients who received surgery for XP. Patients were classified into four grades according to the location and extent of the lesion. Ninety-five cases were reviewed, 70% of which were treated with simple excision in conjunction with blepharoplasty. The remaining 30% were treated with a combination of simple excision and local flaps or skin grafts. These were performed in patients with more advanced grades of the disease. There were no associated complications apart from postoperative scar contracture (4.2%) in patients graded III or IV.^[48] Recurrence was reported in 3.1% of patients at 12 months and this was

found to be irrespective of the grade.^[48] The incidence of recurrence, however, is increased with incomplete excisions and has been reported in the past to be up to 40% after primary surgical excision, 60% after secondary excision, and 80% with bilateral upper and lower eyelid involvement.^[49] The authors advocate that surgical excision should be the mainstay of treatment for XP lesions that involve the deep dermis or infiltrate the underlying muscle.

Other surgical techniques include a combination approach of surgery and chemical peeling. Zarem and Lorincz^[50] recommend superficially excising the xanthelasma lesions using light electrodesiccation followed by the application of topical TCA.

CONCLUSION

Although XP is considered benign, they can cause significant psychological distress due to their associated cosmetic disfigurement.

They can also indicate an underlying plasma lipid disorder in approximately 50% of patients caused by a lipoprotein or apolipoprotein abnormality. Therefore, patients should be screened for underlying causes of hyperlipidemia and may require follow-up for associated morbidities.

XP rarely causes functional problems; however, treatment is usually sought for aesthetic reasons. Unfortunately, recurrence is often seen with all therapeutic modalities and currently a gold-standard long-term treatment option has yet to be established.

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Conflict of interest

There are no conflicts of interest.

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