Cutaneous Lupus Erythematosus Presenting as Persistent Periorbital Edema: A Report of Two Cases

Rocío Cardona*, Eduardo Michelen-Gomez, Mariana Cruz-Manzano and Sheila M. Valentín-Nogueras

Department of Dermatology, UPR School of Medicine, San Juan, Puerto Rico, USA

Abstract: *Background*: Cutaneous lupus erythematosus (CLE) is a chronic, autoimmune, inflammatory disease characterized by a multi-factorial etiology and a spectrum of cutaneous manifestations with variable evolution. Several CLE variants exist with varying clinical and histopathologic features, depending on the extent of epidermal and/or dermal involvement. Persistent, periorbital edema as the sole clinical manifestation of CLE is rarely reported. We report two cases of lupus tumidus presenting with periorbital edema.

Case Presentations: This is the case of two, unrelated, middle-aged patients with a chronic history of periorbital edema whose review of systems were negative for systemic involvement. Physical examination in both cases revealed periorbital, non-tender, erythematous plaques associated with significant non-pitting edema. No epidermal changes were noted. Rheumatologic and thyroid studies were unremarkable. Histopathology in both patients showed a superficial and deep perivascular lymphocytic infiltrate as well as mucin deposition. After a clinical and histopathologic correlation, a diagnosis of CLE in the spectrum of lupus tumidus was made. In both cases, clinical improvement over the course of several weeks was observed with a taper of oral prednisone 40 mg daily and hydrochloroquinine 200 mg twice daily.

Discussion: Several CLE variants exist in a clinical spectrum where cutaneous and histopathologic findings range from predominant epidermal involvement to mostly dermal involvement. Although uncommon, periorbital edema may be the sole manifestation of CLE. It is important to suspect CLE in cases of persistent, periocular edema in order to avoid delays in diagnosis and treatment.

Keywords: Autoimmune diseases, lupus erythematosus tumidus, cutaneous lupus, periorbital edema, lupus tumidus treatment.

INTRODUCTION

Lupus erythematosus is a chronic, autoimmune disease of multifactorial etiology that is associated with a wide range of cutaneous manifestations [1]. Cutaneous lupus erythematosus (CLE) is defined as isolated cutaneous lupus lesions occurring in the absence of systemic lupus erythematosus (SLE) symptoms [2]. A higher incidence and prevalence of CLE exists when compared with SLE, therefore it is important to recognize the diverse cutaneous presentations of LE [2].

The several variants of CLE are characterized by distinct clinical features, and histopathologic findings which vary in terms of location and depth of inflammatory infiltrate, as well as diverse immunofluorescence patterns [3]. Although rare, periorbital edema may be the sole manifestation of CLE with histopathologic findings suggestive of discoid lupus erythematosus, lupus tumidus, lupus profundus, or cutaneous mucinosis [4].

Lupus erythematosus tumidus (LET), a highly photosensitive form of CLE, classically manifests as erythematous, edematous plaques in sun-exposed areas of the skin [5]. However, less common findings such as scalp involvement or periorbital edema have been described in the context of LET [3]. With regards to histopathologic findings, LET presents with a superficial and deep perivascular and peri-adnexal lymphocytic infiltrate, interstitial mucin deposition and edema [6]. Epidermal involvement is rare [6]. Additionally, in contrast to other subtypes of LE, direct immunofluorescence is typically negative in LET [7].

The differential diagnosis of persistent, periocular edema comprises infectious, inflammatory and autoimmune clinical entities, including those within the CLE spectrum. Therefore, a clinical and histopathologic correlation is required for diagnosis. We report two cases of CLE in the spectrum of lupus tumidus presenting solely with persistent, periorbital edema.

CASE #1

A 38-year-old female patient with past medical history of benign thyroid nodules was evaluated due to an 18-month history of bilateral, periorbital edema associated with photophobia and exacerbated by sun exposure. The patient denied other skin lesions or systemic symptoms including breathing difficulties, arthralgia, myalgia, muscle weakness, eyelid ptosis,

*Address correspondence to this author at the Department of Dermatology, University of Puerto Rico School of Medicine, Medical Sciences Campus, PO BOX 365067, San Juan, Puerto Rico 00936-5067, USA; Tel: 787-392-1680; Fax: 787-767-0467; E-mail: rociomcardona@gmail.com

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fever, palpitations or weight loss. She denied application of any topical products or the use of systemic medications.

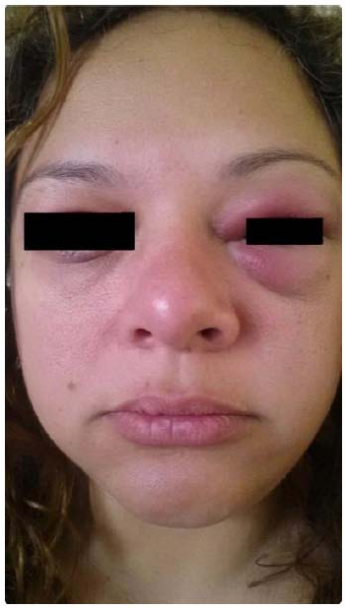


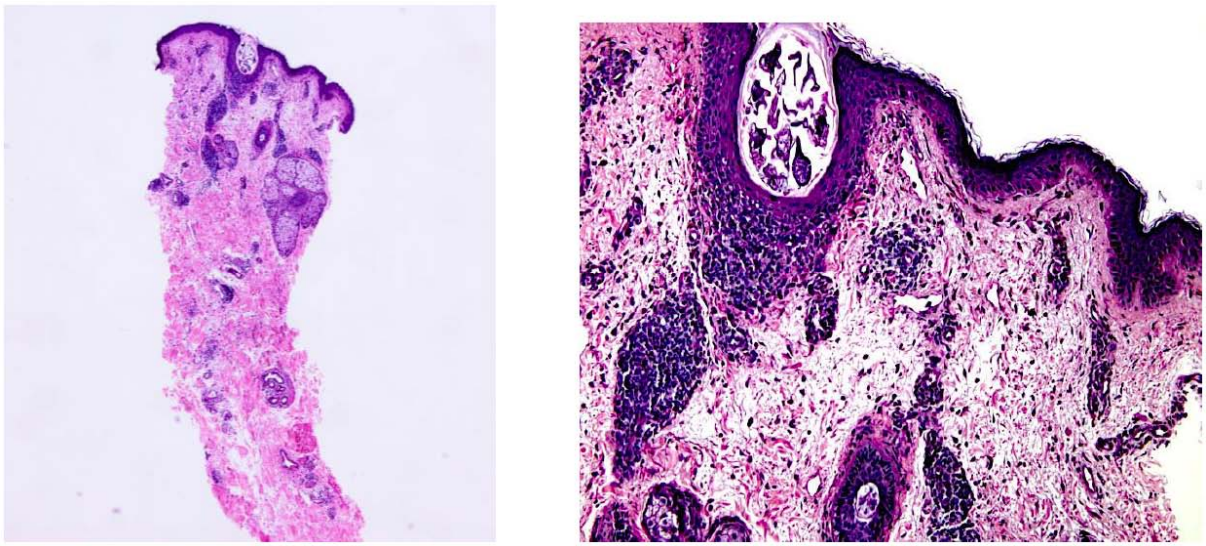
Figure 1: Significant bilateral periorbital edematous plaques.

Prior to presentation, she was evaluated by an allergist who performed an extensive laboratory work-up and prescribed oral prednisolone 10 mg daily for 1 month with mild improvement of symptoms. After discontinuing prednisolone, symptoms recurred and persisted. Physical examination showed bilateral, periorbital, edematous, and erythematous plaques without epidermal changes (Figure **1**). Extraocular eye movements were intact. Cutaneous findings such as heliotrope rash, Gottron's papules, shawl sign, V-neck sign, holster sign or ragged cuticles to suggest dermatomyositis were also absent.

Laboratory work-up including complete blood count (CBC), comprehensive metabolic panel (CMP), urinalysis, IgE levels, thyroid stimulating hormone (TSH), aldolase, anti-dsDNA, anti-Smith, rheumatoid factor (RF), anti-neutrophil cytoplasmic antibody (ANCA), anti-Ro (SSA), anti-LA (SSB), ACE-converting enzyme, and complement levels (C3, C4, C1 inhibitor and C1q) was unremarkable. On the other hand, antinuclear antibody (ANA) titer and erythrocyte sedimentation rate (ESR) level were 1:160 and 25 mm/hr, respectively. Magnetic resonance imaging (MRI) of the brain without contrast showed no abnormalities.

A punch biopsy of the left lower eyelid demonstrated a dense, perivascular and periadnexal lymphocytic inflammatory infiltrate in the superficial and deep dermis with focal vacuolar changes of the basal layer (Figure **2a** and **2b**). Mucicarmine stain (Figure **3**) revealed mucin deposits throughout the dermis. Based on the clinical and histopathologic findings, a diagnosis of lupus erythematosus tumidus was made.

Significant clinical improvement was seen after 2 weeks of therapy with oral prednisone 40 mg daily, hydroxychloroquine 200 mg twice daily, and tacrolimus 0.03% ointment twice daily. Sun protective measures were recommended. At a 7-month follow up, resolution of cutaneous findings was noted without residual scarring or dyspigmentation.



a **b**

Figure 2: a: Superficial and deep perivascular and periadnexal lymphocytic infiltrate (40X); **b**: Periadnexal lymphocytic infiltrate with mild vacuolar changes and melanophages in the papillary dermis; no other significant epidermal changes identified (100x).

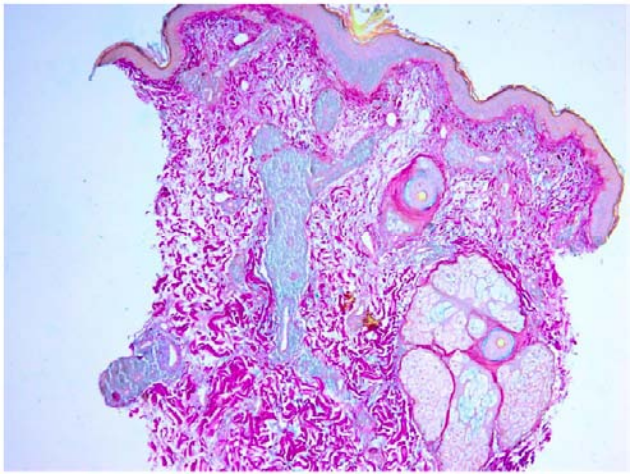


Figure 3: Mucicarmine stain showed mucin deposits throughout the dermis.

CASE #2

A 38-year-old male with no significant past medical history presented with a 6-year history of erythema and edema surrounding his left eye, to the point where he had difficulty keeping his eye open. He denied pain, changes in vision, eyelid ptosis, headache, muscle weakness, or other systemic symptoms. On physical exam, erythematous, edematous plaques were noted involving his left upper and lower eyelids (Figure **4**). No epidermal changes were found. Cutaneous findings such as heliotrope rash, Gottron's papules, shawl sign, V-neck sign, holster sign or ragged cuticles to suggest dermatomyositis were also absent. Conjunctival involvement was absent. Extraocular eye movements were intact.

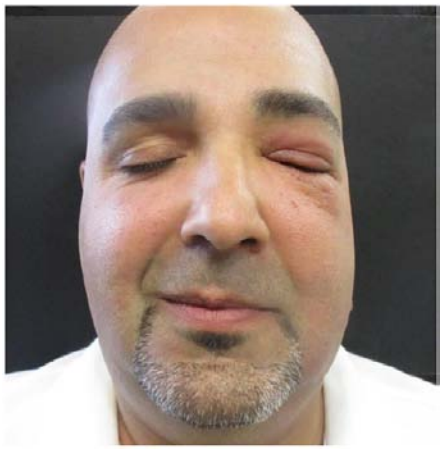


Figure 4: Edematous and erythematous plaques over left superior and inferior eyelids prior to treatment.

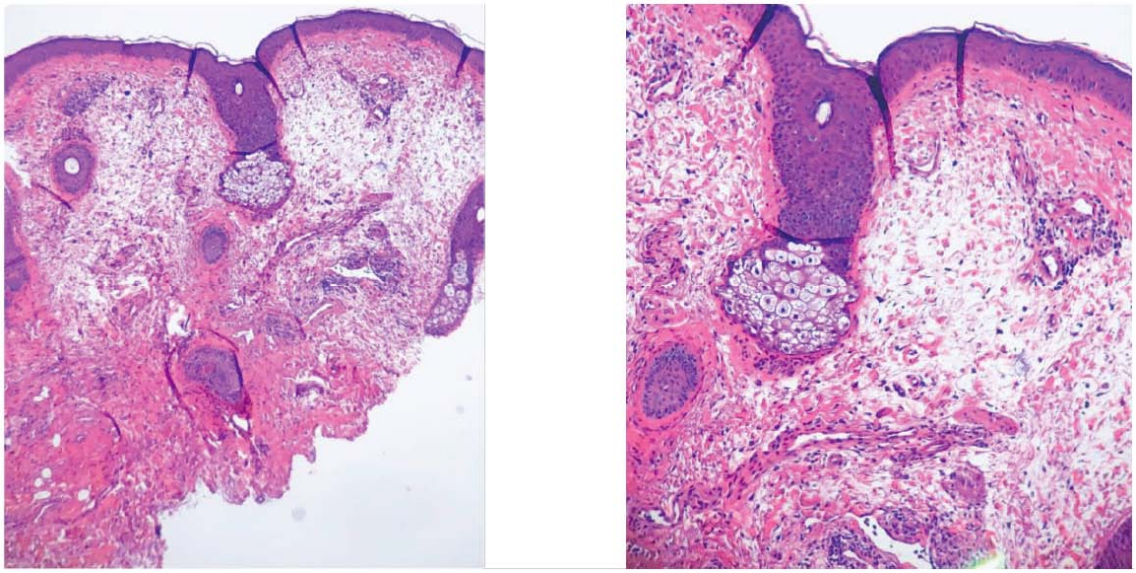
He had been previously evaluated by other services including otorhinolaryngology, allergy and immunology, as well as neurology without significant findings. Laboratory studies such as CBC, CMP, urinalysis and total complement levels including C3 and C4 were within normal limits. Thyroid studies including TSH, free T4/T3 and anti-TPO microsomal antibodies were within normal range. ANA, anti-SSA, anti-SSB, anti-dsDNA, anti-Smith and RF were negative. An MRI of the orbits, with and without contrast, was unremarkable. A punch biopsy of the left lower eyelid showed a superficial and deep perivascular as well as peri-adnexal lymphocytic infiltrate (Figure **5a** and **5b**) with focal vacuolar changes of the basal layer. Dermal mucin deposits (Figure **6a** and **6b**) were also observed. Following a clinical and histopathologic correlation, a diagnosis of lupus erythematosus tumidus was made.

The patient was started on oral prednisone 40 mg daily to be tapered over the course of several weeks, hydroxychloroquine 200 mg twice daily and tacrolimus 0.03% ointment twice daily. Sun protective measures were recommended. Marked clinical improvement was noted following 4 weeks of therapy.

DISCUSSION

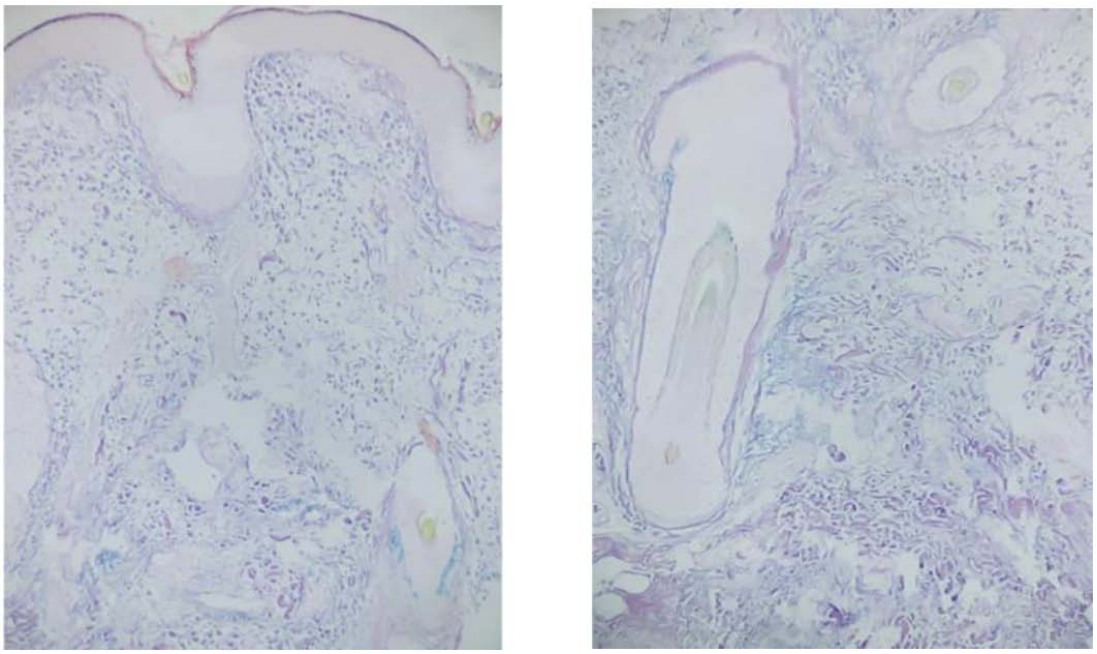
The clinical variants of CLE are contained within a descriptive spectrum also known as the CLE continuum theory, which helps classify them according to the degree of histologic epidermal changes as compared to dermal involvement [8]. Acute cutaneous lupus erythematous (ACLE) can be found at one end of the spectrum of CLE where histopathologic epidermal findings predominate, while lupus erythematous tumidus and papulonodular mucinosis (PNM) associated with SLE are at the opposing end of the spectrum with more prominent dermal involvement [5,8]. Subacute cutaneous lupus erythematous (SCLE) and discoid lupus erythematous (DLE) can be found midway in the aforementioned field. DLE is characterized mainly by dermal changes such as dense, perivascular and periadnexal infiltrate with epidermal changes described to a lesser extent in comparison to SCLE, which is characterized by a higher degree of epidermal changes [5,9].

In patients with SLE, periorbital edema has an overall incidence of 4.8% and only 0.1% of SLE cases debut with this clinical feature [3,10]. Although rare, periorbital edema has been reported as the sole clinical manifestation in cases of CLE (Table **1**) [4,8,10-19]. As observed in our second case, the majority exhibit unilateral involvement (80-84%) with left-side predominance (60%) [18, 20, 21-23, 24, 25]. Although our cases had both upper and lower eyelid



a **b**

Figure 5: a: Hematoxylin and eosin stain with superficial and deep perivascular lymphocytic infiltrate. **b**: Hematoxylin and eosin stain with superficial perivascular lymphocytic infiltrate (100x).



a **b**

Figure 6: a: Mucicarmine stain showed mucin deposits throughout the dermis. **b**: Mucin deposits throughout the dermis (100x).

involvement, 50-72% of cases display upper eyelid involvement [18, 20, 22-25] while others report a predominance of lower eyelid involvement [26]. Most cases of eyelid erythema and edema consistent with CLE have been ultimately classified as DLE [18, 21, 22, 27, 28]. Epidermal atrophy, vacuolar alteration of the basal cell layer, pigment incontinence, lymphohistiocytic perivascular and periappendegeal infiltrate, as well as mucin deposition are a combination of histopathological findings characteristic of CLE, which have been described in the biopsies of patients presenting with periorbital edema [3, 8, 9].

Periocular involvement can be seen as a manifestation of CLE, solid facial edema, Jessner's lymphocytic infiltration (JLI), pseudolymphoma of the skin, allergic contact dermatitis, sarcoidosis, inflammatory myopathies such as dermatomyositis and

Table 1: Cases of CLE Presenting with Periorbital Involvement

Cases of CLE presenting with periorbital involvement								
	Age	**Gender**	**Time to Diagnosis**	**Clinical findings**	**Histopathology**	**Direct Immunofluorescence**	**Diagnosis**	**Treatment and outcome**
Donzis PB, *et al.* (1984)	42 y/o	Male	1 year	Asymptomatic, left peri-orbital edema with violaceous erythema	Consistent with DLE (description of findings not available)	Consistent with DLE (description of findings not available)	DLE	Hydroxychloroquine 200 mg/day. After 4 weeks, periorbital edema had resolved and at 3 months only faint post-inflammatory hyperpigmentation noted.
Cyran S, *et al.* (1992)	51 y/o	Female	4 months	Asymptomatic, left eyelid edema and erythema	Hyperkeratosis, diffuse epidermal atrophy with focal erosion and vacuolization of the basal layer, infundibular follicular epithelium with occasional Civatte bodies, dermal edema, and a moderately dense, superficial and deep perivascular and perifollicular lymphohistiocytic infiltrate	Granular deposition of IgG, IgM, IgA, and C3 along the basement membrane zone	SCLE	Quinacrine 100 mg/d; with marked improvement after 5 weeks. However, the drug was discontinued because of a generalized drug eruption. There were no relapses after 10-month follow-up.
	45 y/o	Female	1 year	Asymptomatic, intermittent, left eyelid edema and erythema	Epidermal atrophy with hydropic degeneration and multiple eosinophilic globules associated with a perivascular and periadnexal lymphohistiocytic infiltrate	Globular fluorescence along the DEJ with IgG, IgM, IgA, and C3	Lupus panniculitis	Hydroxychloroquine 200 mg/d with mild improvement; dose was increased to 400 mg/d and prednisone 40 mg/d was added with complete resolution after 2 months.
Gimenez-Garcia R, *et al.* (2005)	23 y/o	Male	Unknown	Erythema and edema of bilateral lower eyelids	Perivascular and periappendegeal lymphohistiocytic infiltrate associated with parakeratosis, atrophy, and liquefaction of the basal layer	Not performed	DLE	Chloroquine 250 mg/d for 6 months with resolution of symptoms. No relapse after 1year follow-up.
Vassallo C, *et al.* (2005)	38 y/o	Male	3 months	Persistent erythema and edema of the right upper and lower eyelid which worsened with sun exposure	Perivascular and periadnexal lymphocytic infiltrate with focal vacuolar changes and dermal mucin deposits	Granular deposits of fibrinogen and C3 at the basement membrane	Tumid lupus	Hydroxychloroquine 400 mg/d and methylprednisolone 50mg/d with improvement after 1 month. After taper of steroid and antimalarial, the patient relapsed. Thalidomide 100 mg/d for 10 days was started, followed by 200 mg/d for 20 days, and finally 100 mg/d for 2 months without relapse.

(Table 1). Continued.

Cases of CLE presenting with periorbital involvement								
	Age	**Gender**	**Time to Diagnosis**	**Clinical findings**	**Histopathology**	**Direct Immunofluorescence**	**Diagnosis**	**Treatment and outcome**
Ghaninejad H, *et al.* (2006)	23 y/o	Male	1 year	Asymptomatic, bilateral edema of eyelids and cheeks	Superficial and deep perivascular and periadnexal lymphocytic infiltrate with diffuse vacuolar changes and compact hyperkeratosis	Strong, band-like, granular deposition of C3 and IgG at the basement membrane	CLE (no subtype specified)	Chloroquine 150mg BID without improvement; then prednisolone 60 mg/d taper was added with some improvement, but patient relapsed.
	36 y/o	Male	2 years	Erythema and edema on the left side of his face; severe left eye proptosis and prominent periorbital swelling	Epidermal atrophy, focal liquefaction degeneration of basal layer with Civatte bodies, pigment incontinence, and superficial perivascular lymphocytic infiltrate; positive for alcian blue stain for mucin	Diffuse granular deposition of IgG, IgM, C3, and weak deposition of IgA along the DEJ with deposition of immunoreactions on cytoid bodies	CLE (no subtype specified)	Chloroquine 150 mg BID with improvement after 3 months of therapy.
Ricotti C, *et al.* (2008)	38 y/o	Female	5 years	Left lower eyelid edema associated with pain, and epiphora	Interface dermatitis with follicular involvement, superficial and deep perivascular lymphocytic infiltrate, increased dermal mucin confirmed with colloidal iron stain, and significant thickening of the epidermal and adnexal basement membrane confirmed with PAS	Dense granular immunoglobulin M, C3, weaker IgG, and C5b-9 deposits along the epidermal and adnexal basement membrane zone	DLE	Prednisone 40 mg/d with a 4-month taper with concomitant use of mycophenolate mofetil 1g BID and hydroxychloroquine 200 mg BID with significant improvement after 5 months.
Yi-Fang W, *et al.* (2012)	41 y/o	Female	3 years	Erythema and edema of the left upper eyelid	Perivascular and periadnexal lymphocytic infiltrate associated with hyperkeratosis, follicular plugging, vacuolar degeneration, and melanin incontinence; alcian blue positive for mucin	Granular deposition of IgG, IgM, IgA, C3 and C1q in DEJ, dermal vessels, and adnexal structures	DLE	Hydroxychloroquine 400 mg/d and topical steroid cream with improvement after 3 months.

(Table 1). Continued.

Cases of CLE presenting with periorbital involvement								
	Age	**Gender**	**Time to Diagnosis**	**Clinical findings**	**Histopathology**	**Direct Immunofluorescence**	**Diagnosis**	**Treatment and outcome**
Erras S, *et al*. (2012)	26 y/o	Female	3 years	Bilateral edema and erythema of eyelids	Compact hyperkeratosis, diffuse but marked basal cell hydropic degeneration, and superficial and deep perivascular, as well as periadnexal lymphocytic infiltrate	Not performed	CLE (no subtype specified)	Hydroxychloroquine 400 mg/d and prednisone 60 mg/d with improvement after months of treatment; no relapse after 1 year follow-up.
Galeone M, *et al* (2014)	33 y/o	Female	3 years	Well-defined, erythematous patches with partially adherent, whitish scales, over the right lower eyelid margin which worsened with sun exposure. Mild eyelid edema also present	Epidermal atrophy, vacuolar degeneration of basal layer, superficial and deep lymphohistocytic infiltrate in perivascular and periadnexal pattern, and thickening of basement membrane seen with Periodic acid-Schiff stain (PAS)	Not performed	DLE	Hydroxychloroquine 200 mg/d with resolution after 11 weeks of treatment.
Makeeva V, *et al.* (2016)	40's	Male	7 months	Bilateral, persistent periorbital edema	Superficial and deep lymphocytic infiltrate perivascular and periadnexal infiltrate with increased dermal mucin	Not performed	Tumid lupus	Prednisone 40 mg/d with tapering over 2 months and hydroxychloroquine 400 mg/d with improvement and no relapse after 1 year follow-up.
Darjani A, *et al.* (2016)	38 y/o	F	1 year	Left upper eyelid edema and erythema with scale and crust Non-tender although accompanied by pruritus and photophobia	Epidermal atrophy, mild focal parakeratosis, marked basal vacuolar damage, focal basement membrane thickening, capillary dilatation, superficial and deep perivascular lypmhoplasma cell infiltrate with periadnexal perineural involvement. Alcian blue was negative for mucin deposition.	Granular antibody deposits along the dermoepidermal junction of mostly IgG, IgM, C3, C4 and few IgA (positive lupus band test)	DLE	Hydroxychloroquine 400 mg/d with photo-protection. Moderate improvement noted 3 months later.
Chomiciene A, *et al.* (2017)	67 y/o	F	4 months	Asymptomatic, edematous bilateral periorbital area with erythematoviolaceous patches	Epidermal atrophy, vacuolar changes, focal necrosis of basal keratinocytes, massive periadnexal and perivascular lymphocytic infiltration, lichenoid pattern in basal layer of epidermis and around hair follicle epithelium	Not performed	DLE	Hydroxychloroquine 400 mg/d with slight effect after 6 months. Then Tacrolimus 0.1% ointment was added with only slight erythema without swelling remaining. Photoprotection and sun avoidance recommended. 1 year follow-up with good response to treatment.

CLE= Cutaneous Lupus Eryhtematosus; DLE= Discoid Lupus Erythematosus; SCLE= Subacute Lupus Erythematosus

overlap myositis, myxedema, infectious causes such as cellulitis, drug reactions, and angioedema, among others. Our patients did not meet the diagnostic criteria for SLE due to lack of systemic symptoms, and hematologic and serologic abnormalities. In both cases, focal vacuolar changes of the basal layer were noted, which is a common finding in DLE. Even though these changes are seen in DLE, they also have been commonly reported in lupus tumidus [8,17, 29]. Furthermore, the prominent mucin deposition associated with the absence of epidermal atrophy, hyperkeratotic scales, basal membrane thickening and lack of scar and hypopigmented lesions upon resolution, excludes the diagnosis of DLE and SCLE. Although lupus profundus, has also been known for presenting with periorbital edema and erythema, absence of subcutaneous lymphocytic infiltrate excludes this diagnosis [10)]. In contrast to other subtypes of LE, direct immunofluorescence (DIF) is typically negative in LET [7]. In both of our cases, DIF was deferred given initial histopathology findings with hematoxylin and eosin stain were more consistent with CLE in the lupus tumidus erythematosus spectrum rather than the other CLE variants. Although, DIF can be considered when H&E findings are equivocal. Histopathology in dermatomyositis can resemble that of lupus erythematosus [30], but findings for dermatomyositis are usually subtler with epidermal atrophy, sparse superficial and deep perivascular lymphocytic infiltrate, vacuolar interface changes, necrotic keratinocytes as well as mucin deposition [31]. The other main possible diagnosis, JLI and pseudolymphoma of the skin, can be excluded by histopathology showing abundant interstitial mucin deposition [5]. After reviewing the clinical and histopathologic findings of both our cases, particularly the mucin deposition throughout the dermis, a diagnosis of lupus tumidus was given.

The management of CLE includes both topical and systemic medications. Although multiple systemic therapies, such as antimalarials, corticosteroids, methotrexate, retinoids, dapsone, and thalidomide, have been reported with variable success, the antimalarial drugs remain the treatment of choice for CLE patients presenting with periorbital edema [4, 8,10, 15, 29, 32, 33]. In both our cases, significant improvement of skin findings was observed with hydroxychloroquine. Delays in diagnosis of approximately two to three years have been reported in cases of periorbital involvement, with associated ocular complications such as ectropion, conjunctivitis, entropion, and symblepharon [8,15,32,33]. For this reason, prompt diagnosis and treatment is warranted [9, 29, 32].

CONCLUSION

It is rare to encounter periorbital edema as the sole clinical manifestation of CLE. To prevent delays in treatment and possible long-term complications, it important to include CLE as part of the differential diagnosis of persistent, periorbital edema. If physicians' suspect CLE as the underlying cause of periocular edema, clinical and histopathologic correlation is necessary to provide a timely diagnosis. Furthermore, close follow-up is warranted to monitor for other cutaneous or systemic manifestations of LE.

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