RHEUMATOLOGY

Rheumatology 2022;00:1–12
https://doi.org/10.1093/rheumatology/keac231
Advance access publication 12 April 2022

Review

Chilblains in immune-mediated inflammatory diseases: a review

Shirish Dubey [1,2,*], Nilay Joshi[3,*], Olivia Stevenson[3] Caroline Gordon [4] and John A. Reynolds [5,6]

Abstract

Chilblains were first described over a hundred years ago as cutaneous inflammatory lesions, typically on the digits, occurring on cold exposure. Chilblains can be primary, or secondary to a number of conditions such as infections, including COVID-19, and immune-mediated inflammatory disorders (IMIDs) with SLE being the commonest. Chilblain lupus erythematosus (CHLE) was first described in 1888 as cold-induced erythematous lesions before the terms 'chilblains' or 'perniosis' were coined. Diagnostic criteria exist for both chilblains and CHLE. Histopathologically, CHLE lesions show interface dermatitis with perivascular lymphocytic infiltrate. Immunofluorescence demonstrates linear deposits of immunoglobulins and complement in the dermo-epidermal junction. This narrative review focuses on chilblains secondary to immune-mediated inflammatory disorders, primarily the epidemiology, pathogenesis and treatment of CHLE.

Key words: Chilblains, chilblain lupus erythematosus, CHLE, immune-mediated inflammatory diseases, IMID

REVIEW

Rheumatology key messages

- Chilblains can be secondary to many different inflammatory conditions, SLE is the commonest (CHLE).
- CHLE is differentiated from idiopathic chilblains by characteristic changes on histopathology and immunoflourescence.
- Pentoxifylline and tadalafil appear to have good efficacy in primary chilblains.

Introduction

Chilblains are cutaneous inflammatory lesions commonly occurring on exposure to cold and damp conditions. Symptoms develop 12–24 h after a triggering event and characteristically present with burning, painful, pruritic, erthrocyanotic lesions involving extremities. Typically, the lesions are oedematous, tender plaques or papules with purple discolouration or nodules (which may develop central erosions/ulceration) which begin as a pruritic area later becoming tender [1–3]. If located on the soles of the foot, the lesions tend to develop necrosis more rapidly [4]. Involvement of ears and nose is uncommon, as are lesions on the trunk [5].

The term 'chilblain' is of Anglo-Saxon origin, referring to 'chill' for cold and 'Blegen' for sore [6]. Chilblains are also known as perniosis and were first described in 1912. Perniosis is a more general term applied to chilblain lesions, mainly when they occur in the absence of lupus erythematosus (LE) or another immune-mediated inflammatory disorder (IMID) [2, 3, 7]. Perniosis should not be confused with the term 'lupus pernio', which is a misleading name used for cutaneous sarcoidosis and was first described in 1959 [8].

Chilblains can be primary or secondary. Secondary chilblains are associated with IMIDs, infections (including hepatitis), haematological disorders, malignancy and drug-related causes. By far, the most common association is with SLE [4, 9–12] although since 2020, chilblains have been reported in association with COVID-19 [13].

[1]Department of Rheumatology, Oxford University Hospitals NHS FT, [2]Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, [3]Department of Rheumatology, Kettering general Hospital NHS FT, Kettering, [4]Rheumatology Research Group—Institute of Inflammation and Ageing (IIA), [5]John A Reynolds Rheumatology Research Group, Institute of Inflammation and Ageing (IIA), University of Birmingham and [6]Rheumatology Department, Sandwell and West Birmingham NHS Trust, Birmingham, UK

Submitted 2 February 2022; accepted 28 March 2022

Correspondence to: Shirish Dubey, Department of Rheumatology, Oxford University Hospitals NHS FT, Windmill Road, Oxford OX3 7LD, UK. E-mail: shirish.dubey@ouh.nhs.uk

*Shirish Dubey and Nilay Joshi contributed equally to this study.

Table 1 Conditions associated with chilblains

Primary
Idiopathic
Secondary
IMIDs
Systemic lupus erythematosus [4, 11, 12] including sporadic and familial forms
Antiphospholipid syndrome [14, 15]
Behcet's disease [15]
Cryoglobulinemia [7, 16–19]
Cold agglutinin [20]
Infections
Hepatitis B and C [21, 22]
Covid-19 [13]
Haematological and malignancy
Acute lymphoblastic leukemia [23]
Chronic myelomonocytic leukemia [24]
Monoclonal gammopathy of undetermined significance [21]
Leukemia cutis [25]
Lymphoma [26]
Drug induced
Sulindac [27]
Infliximab [28] and other anti-TNF agents [29]
Others
Post traumatic perniosis [30]
Pregnancy [31]

In primary chilblains, the lesions often resolve within a few days to three to four weeks [5]. Persistence of lesions, appearance in warmer temperatures or unusual features such as ulceration or scarring should lead to a search for a secondary cause [9, 10]. A full list of conditions associated with chilblains is shown in Table 1.

Chilblain lupus erythematosus (CHLE) is an uncommon variant of cutaneous LE first described by Jonathan Hutchinson in 1888 as cold-induced erythematous lesions. He had initially termed it 'Lupus Pernio' 24 years before the initial description of primary chilblains [11]. Millard and Rowell classified these lesions as chilblain lupus erythematosus of Hutchinson's; they can be a symptom of cutaneous lupus erythematosus (CLE) SLE [5]. Raynaud's-associated discolouration can occur concomitantly with CHLE lesions in some cases. CHLE can occur in the context of SLE and is a specific subtype of chronic cutaneous LE in the SLICC 2012 Classification Criteria for SLE [12]. In a prospective study of 33 patients affected by severe chilblains, Viguier *et al.* proposed that persistence of lesions during hot seasons was an important feature that could delineate CHLE from idiopathic chilblains [9].

The purpose of this narrative review is to describe the epidemiology, management and complications of chilblains secondary to IMIDs.

Methods

Search strategy: This review was supported through a MEDLINE and Embase search (29 April 2021) using the terms: ('chilblains' OR 'pernio' OR 'chilblain' OR 'perniosis' OR 'acrosyndrome'). Our initial search identified 334 articles in the English language; the titles and abstracts of these were reviewed for inclusion in the review. Because there are limited clinical trials in this area (and no randomized controlled clinical trials in CHLE), we also included case reports of treatments that had been effective. Publications that did not provide any new information were not referenced. This led to the identification of 49 articles selected on the basis of their relevance and originality. Additional manuscripts, including those describing COVID-19 and immune-mediated inflammatory conditions with skin lesions such as SLE were identified through searches of cited articles or through personal contact.

Results

With the exception of CHLE, there is paucity of data on the occurrence of chilblains in other IMIDs, therefore the results focus on CHLE.

Incidence/prevalence

A small study by Takci *et al.* including 51 patients reported that the majority (86%) of chilblains seen in a dermatology outpatient department were primary and only 14% secondary to another cause such as a connective tissue disorder or hepatitis [21]. Conversely, Yell *et al.* report that 15/73(20.5%) of SLE patients had chronic CHLE [32]. Gold had reported in 1960 that 3% of discoid LE patients had chilblains [33]. There is paucity of good quality epidemiological data on secondary chilblains and CHLE. Hedrich *et al.* reported that an estimated 20% of patients with CHLE will go on to develop features of SLE, although this was based on only 17 patients [7]. A French study of 50 consecutive patients with SLE and digital cutaneous lesions identified CHLE in 15 (30%) of patients, and also reported progression to SLE in ∼18% of patients [34]. In contrast, CHLE has been quoted as being present in about 6% of patients with SLE, predominantly females [5]. Although some reports suggest that CHLE is commoner in females [5], others indicate that there is no sex difference when secondary chilblains are considered together [22]. Familial CHLE is rare, and reports are typically limited to small families, and is discussed in more detail below.

Pathogenesis

The pathogenesis of CHLE is not well understood. Vasoconstriction provoked by exposure to cold leads to the occlusion of the capillary bed and a circulation slowdown with the presence of aggregates of red blood cells visible on capillaroscopy [5, 35]. Antibodies to Ro/SSA may be demonstrated in a subset of CHLE patients [35]. However, in patients with SLE, Bouaziz *et al.* did not find association with anti-Ro antibodies [34]. Full-thickness skin grafts from unaffected regions resulted in persistent improvement in two reported cases, implying that local factors might be crucial in the pathophysiology [36].

Familial chilblain lupus (FCL) can arise due to loss-of-function mutations in TREX1, or less commonly SAMHD1, or gain-of-function mutations in TMEM173 (which encodes stimulator of interferon genes, STING). TREX1 is a 3'-to-5' DNA exonuclease which clears single and double stranded DNA in the cytoplasm. Defects in TREX1 lead to increased activation of the cGAS/STING pathway and subsequently increased expression of type 1 IFNs [37–41]. Enhanced 1 IFN responses may therefore also be important in COVID-19-associated chilblains in which there are also high levels of type 1 interferon (IFN) as part of the antiviral response [42]. FCL has onset in childhood and may improve with age which contrasts with sporadic CHLE which is usually observed in middle-aged women [7]. Mutations in TREX1, SAMHD1 and TMEM173, along with RNASEH2A/B/C, ADAR and IFHI1, are also associated with Aicardi-Goutières syndrome (AGS) which can cause retinal vasculopathy with cerebral leukodystrophy; up to 40% of patients with AGS experience CHLE-like lesions [1, 37–40]. Chilblains or chilblain-type lesions have been described quite frequently following development of COVID-19 [13, 43]. COVID-19 toes/pseudo-chilblains seem to occur predominantly in children and young adults and appear to be a relatively late feature of COVID-19 [44, 45]. Livedo or necrosis, with lesions suggesting occlusive vascular disease usually affects people with more severe COVID-19 while chilblains might be associated with less severe manifestations of COVID-19 [14, 46]. Histological studies suggest that chilblain-type lesions are associated with microthrombi [47]. Microhaemorrhages, pericapillary oedema and dilated capillary loops were observed on capillaroscopy [47]. A causative link between chilblains and COVID-19 remains inconclusive, especially since cold exposure does not appear to be a precipitating factor [48].

Diagnosis

Chilblains are generally diagnosed on clinical grounds with supporting histopathology in some cases (see Fig. 1).

Diagnostic criteria have been proposed by the Mayo clinic for both CHLE (based on five patients in 1994) [10] and idiopathic chilblains [49]. To diagnose definite CHLE, patients must fulfil both the major criteria and at least one of the minor criteria (Table 2).

Some immunological anomalies are frequently observed (although not necessary for diagnosis) in CHLE, including hypergammaglobulinemia (>2/3 of patients), positive RF (~50%), ANA, anti-Ro/SSA, and antiphospholipid (APL) antibodies [5, 7, 50]. Skin biopsy can be helpful in diagnosis (see below).

Differential diagnosis

There is a broad range of differential diagnoses that one needs to consider (see Table 3).

Fig. 1 Patient photo of CHLE lesions on the foot and also demonstrating splinter haemorrhage

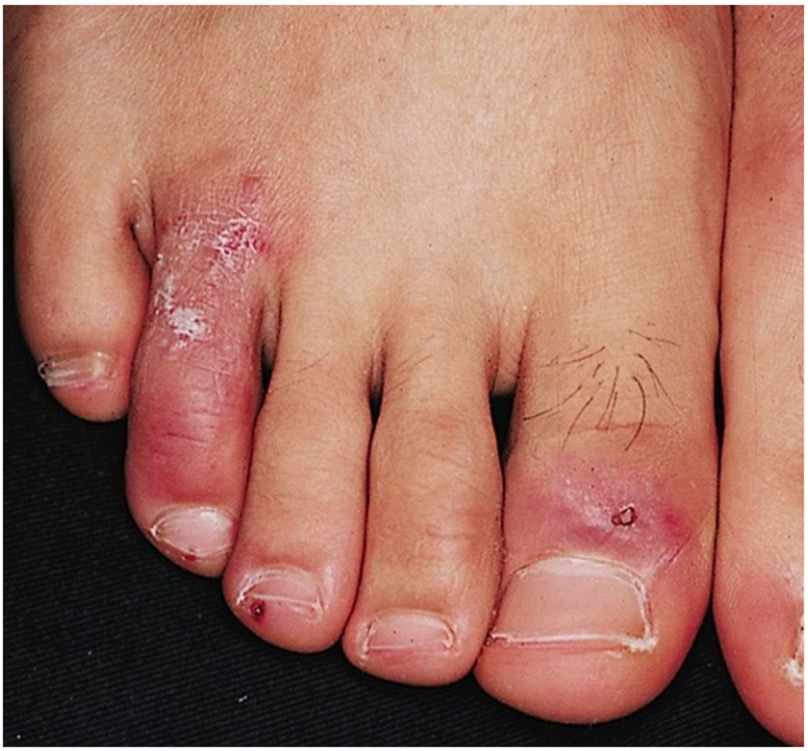


Table 2 Diagnostic criteria for CHLE proposed by Mayo clinic

Two major criteria:
1. Skin lesions of acral sites induced by exposure to cold or a drop in temperature.
2. Evidence of lupus erythematosus in the skin lesions, as determined by histopathologic examination or direct immunofluorescence.
Three minor criteria:
1. Coexistence of systemic lupus erythematosus (SLE) or other skin lesion of discoid lupus erythematosus.
2. Response to anti-lupus therapy.
3. Negative cryoglobulin and cold agglutinin studies.
Patients must fulfil both major criteria and at least one of the minor criteria to be diagnosed as having definite CHLE.

Table 3 Differential diagnosis of chilblains

Frostbite and cold urticaria	are not confined to the extremities and can be reproduced by the ice cube test.
Acrocyanosis	is permanent and painless. It presents with chronic coolness and violaceous discolouration of extremities.
Erythromelalgia	evolves in paroxysmic crisis and is characterized by the triad of burning pain, recurrent redness and warmth of the extremities. These symptoms occur during exposure to heat, during exercise and in response to gravity and can be relieved by cooling and elevation.
Raynaud's phenomenon	is ischaemic discolouration of fingers, toes, nose, etc on exposure to cold, stress or emotional upset due to spasm of blood vessels with vasodilatation and hyperaemia on removal of the stimulus.
Vasculitis	Is purpuric and more necrotic and is often associated with systemic symptoms but is easily confused with chilblains.
Cold panniculitis	is common in young children is a form of lobular panniculitis that results from direct cold exposure. It typically occurs on cheek and chin. Erythematous, indurated plaques develop at the sites of cold exposure and resolve within a few weeks. In this condition, biopsy show lobular panniculitis and a superficial and deep perivascular lymphohistiocytic infiltrates.
Blue toe syndrome	embolism-induced ischaemia including blue toe syndrome can often present with distal blue discolouration of a digit and can involve hands or feet.
Cryofibrinogenemia	can cause cryopathy that can lead to cold intolerance, Raynaud phenomenon, purpura, or livedo reticularis and in severe cases skin necrosis, acral ulcers and gangrene.
Lupus pernio	cutaneous sarcoidosis can present various types of lesions some of which are reddish purple nodules that may occur at a peripheral site, but usually in the face or nose.
Achenbach syndrome	is a benign condition associated with spontaneous bruising over the fingers along with burning pain usually on volar aspect of the hand.
Thromboangiitis obliterans or Buerger's disease	is a rare inflammatory condition affecting young or middle-aged smoking men causing distal ischaemia and sometimes necrosis.

Histopathology

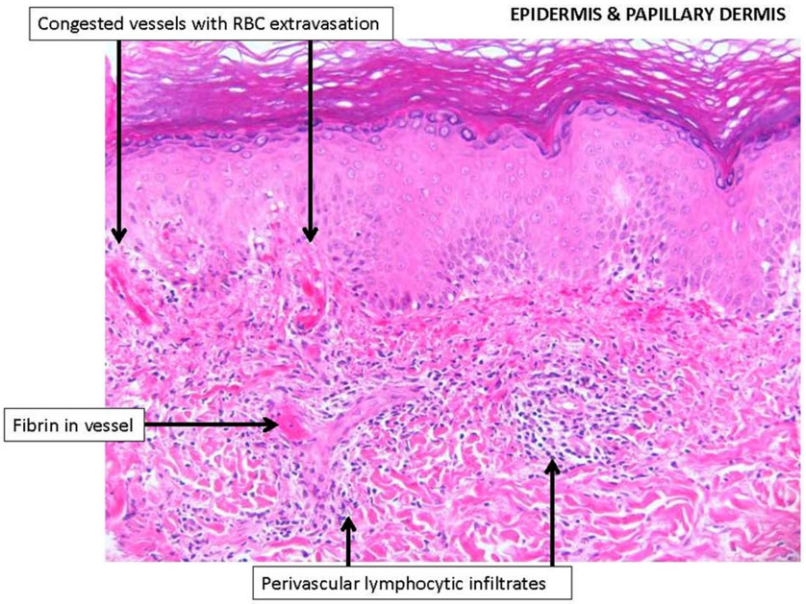
A skin biopsy may be useful in confirming as CHLE has specific pathological features that can help to differentiate CHLE from idiopathic chilblains and other skin lesions. Biopsies in idiopathic chilblains demonstrate an interface dermatitis, superficial and deep perivascular lymphocytic infiltration with deep perieccrine reinforcement and dermal oedema. The epidermal changes include orthohyperkeratosis, necrotic keratinocytes and variable atrophy [5, 51–53]. In CHLE, as opposed to idiopathic chilblains, epidermal spongiosis and perieccrine inflammatory infiltrate are not commonly seen [51]; however, there is vacuolization of the basal layer of epidermis [9, 10, 53] (Figs 2 and 3). Wang *et al.* reported a case-control study of 39 patients with idiopathic chilblains and 20 patients with CHLE. This study identified that increased dermal interstitial mucin deposition and fibrin exudate may help in distinguishing CHLE from idiopathic chilblains [54]. Studies with immunofluorescence have demonstrated that CHLE lesions are typified by linear deposits of immunoglobulins and complements in the dermo-epidermal junction, similar to discoid lupus; Table 4 describes the principal differences between idiopathic chilblains and CHLE [10]. There remain concerns about doing biopsies in patients with vasospastic conditions and impaired peripheral circulation, which reduces our understating of the etiopathogenesis and thereby treatment.

Immunohistochemistry is not helpful in distinguishing idiopathic chilblains from CHLE. In both idiopathic chilblains and CHLE the infiltrate shows CD3+ T cells associated with CD68+ macrophages and a few CD20+ B lymphocytes. A similar percentage and distribution of CD123 + cells in idiopathic pernio and CHLE is seen [51, 54].

Treatment

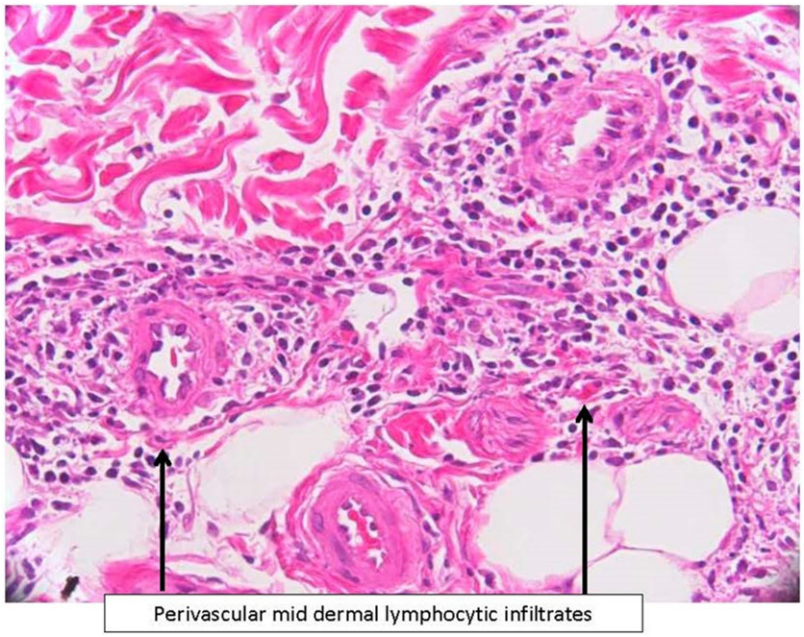
Although chilblain lesions may respond to conservative measures, in refractory, recurrent or severe lesions, pharmacological interventions may be necessary [7]. The treatment aim in CHLE is to prevent development of new lesions and expedite the healing of current lesions to reduce discomfort and avoid scarring.

Fig. 2 Skin biopsy appearances under low magnification



Histopathological features of CHLE on skin biopsy (×100 magnification, haemotoxylin and eosin staining) demonstrating RBC extravasation, fibrin in vessel and perivascular lymphocytic infiltrate.

Fig. 3 Skin biopsy appearances under higher magnification



Histopathological features of CHLE on skin biopsy (×400 magnification, haemotoxylin and eosin staining) demonstrating perivascular mid-dermal lymphocytic infiltrates.

Conservative management

Conservative management includes avoidance of cold and damp, and use of insulated clothing, gloves and footwear [7]. There are no studies assessing the impact of these measures.

Pharmacological

The majority of studies describing treatment of chilblains are focussed on primary chilblains. There are no randomized controlled trials (RCTs) of any agent in secondary chilblains. The majority of trials have included

TABLE 4 Pathology and differences between primary and secondary chilblains

	Idiopathic	CHLE
Histology	Dermal oedema with mixed immune infiltrate invading papillary and or reticular dermis. Inflammatory infiltrate is composed of mononuclear cells, mainly lymphocytes. Necrotic keratinocytes are seen, but commoner in idiopathic. Inflammation typified by perieccrine distribution. Epidermal spongiosis may contain necrotic keratinocytes. Vascular microthrombi can be found in the dermis. Papillary dermal oedema commonly seen.	Perieccrine inflammation not typically seen. Epidermal spongiosis not typically seen.
Immunopathology		Vacuolization of the basal layer of the epidermis is commonly seen. Perivascular lymphocytic infiltrates and lymphocytic vasculitis in both superficial and deep layers seen. Deposits of complement and immunoglobulins at dermo-epidermal junction.
Immunohistochemistry	Dermal interstitial fibrin exudate and mucin: less common. Infiltrate: mainly of CD3+T cells associated with CD68+ macrophages and a few CD20+B lymphocytes. Similar percentage and distribution of CD123+ cells in idiopathic chilblains and CHLE.	Dermal interstitial fibrin exudate and mucin: common.

relatively small numbers of patients with short follow-ups, heterogeneous outcomes and no data on recurrence and longer-term outcomes. As there are no trials in secondary chilblains, extrapolation of limited data in primary chilblains may be helpful. We identified RCT data for nifedipine, pentoxifylline, prednisolone and tadalafil in primary chilblains. The key findings from trials are summarized in Table 5.

Topical treatments

Topical corticosteroids do not appear to be particularly effective, although may be of some benefit [7, 49, 55]. Topical glyceryl trinitrate (GTN) 0.4% was found to be similar in efficacy to nifedipine (initially 10–20 mg daily, increased to 20–40 mg daily) in a single-blind randomized trial, although resolution was slower in the GTN arm [57]. Topical tacrolimus and pimecrolimus have been used anecdotally with some benefit [7, 66].

Systemic treatments

Vasodilators

Nifedipine has inconsistent evidence in the treatment of primary chilblains. Studies suggest superiority to placebo in some studies but not others [56–60], with reports of superiority to diltiazem [61] and topical 5% minoxidil solution [62].

Pentoxifylline

Pentoxifylline is a xanthine derivative that non-selectively inhibits phosphodiesterase and has been shown to decrease blood viscosity and improve erythrocyte flexibility, which have been postulated to be an important factor in the pathogenesis of chilblain lesions [67]. It has demonstrated superiority to placebo [63, 65], oral prednisolone and topical clobetasol [64] in studies.

Tadalafil

Tadalafil is a selective phosphodiesterase type 5 (PDE5) inhibitor with a long half-life (17.5 hours). An open-label study demonstrated superiority over both pentoxifylline and prednisolone in terms of lesion severity after 2 weeks [65].

Immunomodulators and immunosuppressive agents

Prednisolone

As described above, in randomized controlled trials, oral prednisolone has been shown to be inferior to both pentoxifylline and tadalafil in primary chilblains [64, 65].

Chloroquine or HCQ

There are no randomized controlled trials of HCQ or chloroquine in CHLE. In 1912, Chipman *et al.* were the first to report use of anti-malarials for perniosis. Quinine

Table 5 Summary of clinical trial data in chilblains

Study type, location, type of CB, year of publication	Intervention	Comparator	Numbers recruited (completed)	Outcome	Limitations
Topical corticosteroids					
Randomized placebo-controlled crossover trial, Netherlands, Primary, 2017 [55]	Betamethasone valerate (BMV) 0.1% cream twice daily for 6 weeks	Placebo	34–19 in intervention, 15 in placebo, no dropouts	No difference in outcomes VAS over 13 weeks	Study size
Vasodilators: calcium channel blockers					
Randomized placebo-controlled crossover trial, England, primary, 1986 [56, 57]	Nifedipine retard 20 mg PO TID for 6 weeks	Placebo	10 in both arms	Positive nifedipine: 7/10 patients (70%) in the nifedipine group had resolution of lesions within 10 days (*vs* 20-28 days with placebo), and no new lesions developed while on treatment. Five patients initially treated with placebo relapsed within one week of starting placebo. For 3/5 patients (60%) in the placebo group, code was broken due to relapse severity and nifedipine was restarted with good response.	Study size
RCT, India, unspecified, 2003 [58]	Nifedipine (plain) 10 mg PO TID until complete relief and then nifedipine extended release 20 mg PO daily (total duration 21 days)	Diltiazem 60 mg PO TID for 21 days	21 patients in nifedipine arm, 12 in diltiazem arm	Positive nifedipine: 21/24 patients (88%) in the nifedipine group showed 80% to 90% improvement by the 14th day, *vs* only 5/12 patients (42%) in the diltiazem group. 7/12 (58%) who had no response to diltiazem were switched to the nifedipine group between days 7 to 10.	Study size, blinding and type of chilblains not specified
RCT single blind, Pakistan, primary, 2014 [59]	Nifedipine retard 10–20 mg PO daily for 1 week, then 20–40 mg PO daily for 5 weeks if tolerated	Topical GTN (0.4%) cream applied twice daily for 6 weeks	34 (27) in nifedipine arm, 31 (26) in GTN arm	Positive nifedipine: Nifedipine group achieved earlier clearance compared with GTN cream (10.9 +/– 6 days *vs* 16.6 +/– 11.5 days, $P = 0.05$).	Study size, blinding, ~18% dropout
RCT single blind, Iraq, primary, 2010 [60]	Nifedipine sustained release 20 mg PO daily for 1 week, followed by 20 mg PO BID for 1 week	Topical 5% minoxidil solution applied twice daily for 2 weeks	42 (35) patients in nifedipine arm, 20 (17) patients in minoxidil arm	Positive nifedipine: 20 patients (57%) in the nifedipine arm showed good improvement, 9 (25%) very good improvement, compared with six patients (35%) with good improvement and one patient (6%) with very good in the minoxidil group ($P < 0.05$).	

(continued)

Table 5 Continued

Study type, location, type of CB, year of publication	Intervention	Comparator	Numbers recruited (completed)	Outcome	Limitations
Randomized placebo-controlled crossover trial, Netherlands, primary, 2016 [61]	Nifedipine controlled release (CR) 30 mg PO daily for 2 weeks, followed by nifedipine CR 30 mg PO BID for 4 weeks	Placebo	32(32)	No difference: After 6 weeks of treatment, mean scores on the VAS on symptoms showed no significant difference between nifedipine and placebo ($P = 0.44$). VAS on disability also no significant difference ($P = 0.75$).	
RCT, open label, India, primary, 2018 [62]	Nifedipine 10 mg PO daily and oral antihistamines for 2 weeks	Topical 5% minoxidil gel twice daily and oral antihistamines for 2 weeks	42 in each, all completed	Positive nifedipine: 10/42 patients (23.8%) in the nifedipine group *vs* 3/42 patients (7%) in the minoxidil group showed very good improvement ($P = 0.001$).	
Vasodilators: other					
RCT, Iraq, primary, 2008 [63]	PTX 400 mg PO TID for 2 weeks	Prednisolone 2.5 mg/kg PO BID and clobetasol ointment for 2 weeks	20 (9) in pentoxifylline group, 20 (11) in corticosteroid group	Positive PTX: Prednisolone and clobetasol group 3/11 (27%) who completed treatment had 'good improvement', compared with 5/9 (56%) in the PTX group ($P < 0.05$).	Study size, very high dropout rate
RCT, open label, Iraq, primary, 2015 [64]	Group A: tadalafil 5 mg PO daily for 2 weeks. Group B: PTX 400 PO TID for 2 weeks Group C: prednisolone 15 mg PO BID for 2 weeks		Group A: 19 (15) Group B: 18 (13) Group C: 21 (19) Overall, 58 (47) patients recruited	Tadalafil > PTX >prednisolone: Percentage improvement in severity score was 50.65, 44.16 and 31.51%, for tadalafil, PTX and prednisolone groups, respectively (ANOVA *P*-value = 0.004).	
RCT, double blind placebo controlled, Iraq, primary, 2016 [65]	PTX 400 mg PO TID for 3 weeks	Placebo	59 (55) PTX 59 (55) Placebo	Positive PTX: 40/55 (72.7%) PTX patients achieved very good response at 3 weeks *vs* 11/55 (20%) placebo patients ($P < 0.0001$).	

BID: twice daily; GTN: glyceryl trinitrate; PO: per oral; PTX: pentoxifylline; RCT: randomized controlled trial; TID: thrice daily; VAS: visual analogue scale.

was suggested as being effective for both SLE and chilblains, although no data are provided in this article [68]. A French meta-analysis of cutaneous manifestations of SLE (Chasset *et al.*) suggested that anti-malarials were less effective in CHLE (response rate 31%) compared to acute cutaneous LE (response rate 91%) [69]. In a retrospective study of five patients by Yang *et al.*, three with primary chilblains and two with SLE, HCQ improved chilblains in four patients which included both patients with SLE [70]. Patel and Hardo and Horino *et al.* reported successful use of HCQ in a patient with CHLE [71, 72]. In a case series, Millard and Rowell reported HCQ and chloroquine were of benefit to three patients with CHLE. Discontinuation resulted in relapse of symptoms [5]. In case series of 15 patients, Doutre *et al.* reported that HCQ at 600 mg dosage was effective after 3 months [4]. HCQ was found to be effective in four out of 15 patients with CHLE in a study by Bouaziz *et al.* [35]. Su *et al.* reported that only one in five patients treated with chloroquine saw a complete resolution of lesions within two months [10].

MMF

MMF has been successfully used in recalcitrant CHLE lesions in two cases [73, 74]. Gammon *et al.* reported two cases of CHLE with partial response to MMF as part of an open-label series of 24 patients with different manifestations of CLE [75].

Anecdotal use of other therapies

Due to lack of good quality evidence, a number of different drugs have also been tried in single or more cases and found to be of benefit (more often in primary chilblains). These include:

- Vasodilators: etretinate, diltiazem, amlodipine, phenoxybenzamine, thymoxamine, prazosin (the last three are alpha blockers), nicotinamide and niacin derivative pyridyl carbinol.
- Others: phototherapy, full thickness skin graft [36], chemical lumbar sympathectomy [76], dapsone, vitamin D3 and vitamin K.

The authors are aware of the use of aspirin, together with vasodilators and HCQ in some patients, but we could not find any evidence for this. In CHLE, Raynaud's phenomenon often co-exists with chilblains, so a number of patients with CHLE may be prescribed vasodilators for this indication.

There are no studies looking at long-term outcomes. In CHLE, experience suggests that it tends to fluctuate, and often the lesions recur in the same location. In some patients, there appears to be a correlation between lupus activity and CHLE flares while not in others. However, there are no studies describing this.

Limitations

There are a number of limitations of this review particularly around the paucity and poor-quality data available on all aspects of secondary chilblains.

Conclusions

Chilblains can be secondary to a number of different IMIDs, with SLE being the commonest. Histologically, the skin in CHLE demonstrates lymphocytic vasculitis as well as other features of CLE such as deposition of immunoglobulins and complement in the dermo-epidermal junction. Studies in primary chilblains suggest better response to pentoxifylline and tadalafil compared with topical corticosteroids and nifedipine. Limited data are available on the epidemiology, treatment and long-term outcomes of secondary chilblains. More research is needed to understand the impact of chilblains in IMID patients and also to assess efficacy of pentoxifylline and tadalafil. Combination therapy with aspirin, vasodilators and hydroxychloroquine is also worthy of further study. The role of immunosuppression in CHLE remains unclear and well-designed clinical trials are needed.

Acknowledgements

We wish to thank the library team at Kettering General Hospital for their wonderful help and support with the literature review.

All listed authors provided substantial contributions to this work. S.D. and N.J. were involved with the conception and design. The literature review was led by N.J. with help from S.D. and all the other listed authors. O.S. provided the figures for the article. All authors have contributed to the critical revision of the manuscript and agreed on the final version.

Funding: No specific funding was received from any funding body in the public, commercial and not-for profit sectors to carry out the work described in this study.

Disclosure statement: The authors have declared no conflicts of interest.

Data availability statement

All data relevant to the study are included in the article.

References

1 Külcü Çakmak S, Gönül M, Oğuz ID *et al.* Demographical, laboratory and associated findings in patients with perniosis. J Eur Acad Dermatol Venereol 2014;28:891–4.

2 Dowd PM. Perniosis. In: Champion RH, Burton JL, Burns DA, Breathnach SM, eds. Textbook of dermatology, 6th edn. Oxford: Blackwell Science, 1998: 960.

3 Ryan TJ. Chilblains. In: Freed-berg IM, Eisen AZ, Wolff K *et al.*, eds. Fitzpatrick's dermatology in general medicine, 5th edn. New York: McGraw-Hill, 1999: 1499.

4 Doutre MS, Beylot C, Beylot J, Pompougnac E, Royer P. Chilblain lupus erythematosus: report of 15 cases. Dermatology 1992;184:26–8.

5 Millard LG, Rowell NR. Chilblain lupus erythematosus (Hutchinson). A clinical and laboratory study of 17 patients. Br J Dermatol 1978;98:497–506.

6 Encyclopaedia Britannica, or a dictionary of arts, sciences, and miscellaneous literature, 6th edn. Edinburgh: Archibald Constable and Company, 1823.

7 Hedrich CM, Fiebig B, Hauck FH *et al.* Chilblain lupus erythematosus – a review of literature. Clin Rheumatol 2008;27:949–54. Erratum in: Clin Rheumatol 2008;2: 1341.

8 James DG. Dermatological aspects of sarcoidosis. Q J Med 1959;28:108–24.

9 Viguier M, Pinquier L, Cavelier-Balloy B *et al.* Clinical and histopathologic features and immunologic variables in patients with severe chilblains. A study of the relationship to lupus erythematosus. Medicine 2001;80: 180–8.

10 Su WPD, Perniciaro C, Rogers RS, White JW. Chilblains lupus erythematosus (lupus pernio): clinical review of the Mayo Clinic experience and proposal of diagnostic criteria. Cutis 1994;54:395–9.

11 Hutchinson J. Harveian lectures on lupus: the varieties of common lupus. Br Med J 1888;1:58–63.

12 Petri M, Orbai AM, Alarcón GS *et al.* Derivation and validation of the systemic lupus international collaborating clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum 2012;64:2677–86.

13 Galván Casas C, Català A, Carretero Hernández G *et al.* Classification of the cutaneous manifestations of COVID-19: a rapid prospective nationwide consensus study in Spain with 375 cases. Br J Dermatol 2020; 183:71–7.

14 Lutz V, Cribier B, Lipsker D. Chilblains and antiphospholipid antibodies: report of four cases and review of the literature. Br J Dermatol 2010;163:645–6.

15 Akkurt ZM, Ucmak D, Yildiz K, Yürüker SK, Celik HÖ. Chilblains in Turkey: a case-control study. An Bras Dermatol 2014;89:44–50.

16 Guadagni M, Nazzari G. Acute perniosis in elderly people: a predictive sign of systemic disease? Acta Derm Venereol 2010;90:544–5.

17 Weston WL, Morelli JG. Childhood pernio and cryoproteins. Pediatric Derm 2000;17:97–9.

18 Yang X, Perez OA, English JC 3rd. Adult perniosis and cryoglobulinemia: a retrospective study and review of the literature. J Am Acad Dermatol 2010;62:e21-e22.

19 Gordon R, Arikian AM, Pakula AS. Chilblains in Southern California: two case reports and a review of the literature. J Med Case Rep 2014;22:381.

20 Gönül M, Keseroğlu HO, Kurmuş GI, Han U, Ergin C. A case of pernio associated with cold agglutinin positivity in an unusual location. J Dermatol Res Ther 2016;1: 01–4.

21 Takci Z, Vahaboglu G, Eksioglu H. Epidemiological patterns of perniosis, and its association with systemic disorder. Clin Exp Dermatol 2012;37:844–9.

22 Souwer IH, Lagro-Janssen AL. Chronic chilblains. BMJ 2011;7:342:d2708.

23 Park KK, Tayebi B, Uihlein L, Speiser J, Mir A, Gerami P, Mancini A, Kim W. Pernio as the presenting sign of blast crisis in acute lymphoblastic leukemia. Pediatr Dermatol 2018;35:e74–5.

24 Kelly JW, Dowling JP. Pernio. A possible association with chronic myelomonocytic leukemia. Arch Dermatol 1985;121:1048–52.

25 Al-Niaimi F, Chadha M, Cox N. Leukaemia cutis presenting as digital and chilblain-like perniosis. Eur J Dermatol 2010;20:836–7.

26 Marks R, Baker H, Marten RH, Gold SC. Chilblain lupus erythematosus as a manifestation of lymphoma. Proc R Soc Med 1967;60:494–6.

27 Reinertsen JL. Unusual pernio-like reaction to sulindac. Arthritis Rheum 1981;24:1215.

28 Richez C, Dumoulin C, Schaeverbeke T. Infliximab induced chilblain lupus in a patient with rheumatoid arthritis. J Rheumatol 2005;32:760–1.

29 Sifuentes Giraldo WA, Ahijón Lana M, García Villanueva MJ, González García C, Vázquez Diaz M. Chilblain lupus induced by TNF-α antagonists: a case report and literature review. Clin Rheumatol 2012;31:563–8.

30 Boesjes CM, van Rhijn BD, van Dijk MR, Sigurdsson V. Posttraumatic unilateral perniosis: a case report. JAAD Case Rep 2019;5:909–11.

31 Stainforth J, Goodfield M, Taylor P. Pregnancy-induced chilblain lupus erythematosus. Clin Exp Dermatol 1993; 18:449–51.

32 Yell JA, Mbuagbaw J, Burge SM. Cutaneous manifestations of systemic lupus erythematosus. Br J Dermatol 1996;135:355–62.

33 Gold S. Progress in the understanding of lupus erythematosus. Br J Dermatol 1960;72:231–9.

34 Bouaziz JD, Barete S, Le Pelletier F, Amoura Z, Piette JC, Francès C. Cutaneous lesions of the digits in systemic lupus erythematosus: 50 cases. Lupus 2007; 16:163–7.

35 Franceschini F, Calzavara-Pinton P, Quinzanini M *et al.* Chilblain lupus erythematosus is associated with antibodies to SSA/Ro. Lupus 1999;8:215–9.

36 Aoki T, Ishizawa T, Hozumi Y, Aso K, Kondo S. Chilblain lupus erythematosus of Hutchinson responding to surgical treatment: a report of two patients with anti-Ro/ SS-A antibodies. Br J Dermatol 1996;134:533–7.

37 Günther C, Hillebrand M, Brunk J, Lee-Kirsch MA. Systemic involvement in TREX1-associated familial chilblain lupus. J Am Acad Dermatol 2013;69:e179-e181.

38 Prendiville JS, Crow YJ. Blue (or purple) toes: chilblains or chilblain lupus-like lesions are a manifestation of Aicardi-Goutières syndrome and familial chilblain lupus. J Am Acad Dermatol 2009;61:727-8.

39 Crow Y, Manel N. Aicardi–Goutières syndrome and the type I interferonopathies. Nat Rev Immunol 2015;15: 429–40.

40 König N, Fiehn C, Wolf C, Schuster M, Cura Costa E, Tüngler V, *et al.* Familial chilblain lupus due to a gain-of-function mutation in STING. Ann Rheum Dis 2017;76: 468-72.

41 Decout A, Katz JD, Venkatraman S, Ablasser A. The cGAS–STING pathway as a therapeutic target in inflammatory diseases. Nat Rev Immunol 2021;21:548–69.

42 Schreiber G. The Role of Type I Interferons in the Pathogenesis and Treatment of COVID-19. Front. Immunol 2020;11:595739.

43 de Masson A, Bouaziz JD, Sulimovic L *et al.* Chilblains is a common cutaneous finding during the COVID-19 pandemic: a retrospective nationwide study from France. J Am Acad Dermatol 2020;83:667–70.

44 Colmenero I, Santonja C, Alonso-Riaño M *et al.* SARS-CoV-2 endothelial infection causes COVID-19 chilblains: histopathological, immunohistochemical and ultrastructural study of seven paediatric cases. Br J Dermatol 2020;183:729–37.

45 Kanitakis J, Lesort C, Danset M, Jullien D. Chilblain-like acral lesions during the COVID-19 pandemic ("COVID toes"): histologic, immunofluorescence, and immunohistochemical study of 17 cases. J Am Acad Dermatol 2020;83:870–5.

46 Lee DS, Mirmirani P, McCleskey PE, Mehrpouya M, Gorouhi F. Cutaneous manifestations of COVID-19: a systematic review and analysis of individual patient-level data. Dermatol Online J 2020;26:13030/qt7s34p8rw.

47 El Hachem M, Diociaiuti A, Concato C *et al.* A clinical, histopathological and laboratory study of 19 consecutive Italian paediatric patients with chilblain-like lesions: lights and shadows on the relationship with COVID-19 infection. J Eur Acad Dermatol Venereol 2020;34:2620–9.

48 Vázquez-Osorio I, Rocamonde L, Treviño-Castellano M, Vázquez-Veiga H, Ginarte M. Pseudo-chilblain lesions and COVID-19: a controversial relationship. Int J Dermatol 2021;60:754–6.

49 Cappel JA, Wetter DA. Clinical characteristics, etiologic associations, laboratory findings, treatment, and proposal of diagnostic criteria of pernio (chilblains) in a series of 104 patients at Mayo Clinic, 2000 to 2011. Mayo Clin Proc 2014;89:207–15.

50 Allegue F, Alonso ML, Rocamora A, Ledo A. Chilblain lupus erythematosus and antiphospholipid antibody syndrome. J Am Acad Dermatol 1988;19:908–10.

51 Cribier B, Djeridi N, Peltre B, Grosshans E. A histologic and immunohistochemical study of chilblains. J Am Acad Dermatol 2001;45:924–9.

52 Rémy-Leroux V, Léonard F, Lambert D *et al.* Comparison of histopathologic-clinical characteristics of Jessner's lym-phocytic infiltration of the skin and lupus erythematosus tumidus: multicenter study of 46 cases. J Am Acad Dermatol 2008;58:217–23.

53 Boada A, Bielsa I, Fernández-Figueras MT, Ferrándiz C. Perniosis: clinical and histopathological analysis. Am J Dermatopathol 2010;32:19–23.

54 Wang ML, Chan MP. Comparative analysis of chilblain lupus erythematosus and idiopathic perniosis: histopathologic features and immunohistochemistry for CD123 and CD30. Am J Dermatopathol 2018;40:265–71.

55 Souwer IH, Bor JH, Smits P, Lagro-Janssen AL. Assessing the effectiveness of topical betamethasone to treat chronic chilblains: a randomised clinical trial in primary care. Br J Gen Pract 2017;67:e187–e193.

56 Dowd PM, Rustin MH, Lanigan S. Nifedipine in the treatment of chilblains. Br Med J (Clin Res Ed) 1986;293:923–4.

57 Rustin MH, Newton JA, Smith NP, Dowd PM. The treatment of chilblains with nifedipine: the results of a pilot study, a double-blind placebo-controlled randomized study and a long-term open trial. Br J Dermatol 1989;120:267–75.

58 Patra AK, Das AL, Ramadasan P. Diltiazem vs. nifedipine in chilblains: a clinical trial. Indian J Dermatol Venereol Leprol 2003;69:209–11.

59 Khalid T, Maan Shehzad AM. K. Comparison of efficacy and safety of topical glyceryl trinitrate vs. oral nifedipine in idiopathic perniosis: results of a randomized clinical trial. JPAD 2014;24:342–7.

60 Kubais TA, Hasan AS, Awad KM, Tawfiq EM. Treatment of perniosis with oral nifedipine in comparison with topical 5% minoxidil solution in Iraqi patients: single blind comparative study. Al-Anbar Med J 2010;8:40–6.

61 Souwer IH, Bor JH, Smits P, Lagro-Janssen AL. Nifedipine vs placebo for treatment of chronic chilblains: a randomized controlled trial. Ann Fam Med 2016;14:453–9.

62 Jain AK, Raghavendra KR, Margaankar M. A random comparative therapeutic trial of oral nifedipine v/s topical 5% minoxidil gel in patients of perniosis at a tertiary care center of North-western India. Indian J Clin Exp Dermatol 2018;4:62–5.

63 Noaimi AA, Fadheel BM. Treatment of perniosis with oral pentoxyfylline in comparison with oral prednisolone plus topical clobetasol ointment in Iraqi patients. Saudi Med J 2008;29:1762–4.

64 Noaimi AA, Salman HA, Sharquie KE. Treatment of perniosis with oral tadalafil, pentoxifylline or prednisolone: a therapeutic comparative study. J Fac Med Baghdad 2015;57:210–3.

65 Al-Sudany NK. Treatment of primary perniosis with oral pentoxifylline (a double-blind placebo-controlled randomized therapeutic trial). Dermatol Ther 2016;29:263–8.

66 Wenzel J, Brahler S, Bauer R, Bieber T, Tuting T. Efficacy and safety of methotrexate in recalcitrant cutaneous lupus erythematosus: results of a retrospective study in 43 patients. Br J Dermatol 2005;153:157–62.

67 McNamara DB, Champion HC, Kadowitz PJ. Pharmacologic management of peripheral vascular disease. Surg Clin North Am 1998;78:447–64.

68 Chipman ED. Chilblains. Cal State J Med 1912;10:512–3.

69 Chasset F, Bouaziz JD, Costedoat-Chalumeau N, Francès C, Arnaud L. Efficacy and comparison of antimalarials in cutaneous lupus erythematosus subtypes: a systematic review and meta-analysis. Br J Dermatol 2017;177:188–96.

70 Yang X, Perez OA, English JC 3rd. Successful treatment of perniosis with hydroxychloroquine. J Drugs Dermatol 2010;9:1242–6.

71 Patel S, Hardo F. Chilblain lupus erythematosus. BMJ Case Rep 2013;2013:bcr2013201165.

72 Horino T, Ichii O, Terada Y. Hydroxychloroquine-associated hyperpigmentation in chilblain lupus erythematosus. J Clin Rheumatol 2020;26:e192.

73 Gouillon L, Debarbieux S, Berruyer M *et al.* Chilblain lupus erythematosus treated successfully with mycophenolate mofetil. Int J Dermatol 2017;56: e158–e159.

74 Boehm I, Bieber T. Chilblain lupus erythematosus Hutchinson: successful treatment with mycophenolate mofetil. Arch Dermatol 2001;137:235–6.

75 Gammon B, Hansen C, Costner M. Efficacity of mycophenolate mofetil in antimalarial resistant cutaneous lupus erythematosus. J Am Acad Dermatol 2011;65:717–21.

76 Breathnach SM, Wells GC. Chilblain lupus erythematosus with response to chemical sympathectomy. Br J Dermatol 1979;101:49–51.