

SARS-CoV-2 Vaccination and Chilblain-like Lesions: What Do We Know so Far?

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ABSTRACT **Introduction:** The coronavirus pandemic has caused massive damage to global health care and the economy. The vaccination program has been paced around the globe to return as soon as possible to pre-COVID time. Although all the vaccines have been approved after the rigorous clinical and safety trials, some adverse effects have surfaced and are being reported from different parts of the world. One such side effect is chilblain-like lesions following the COVID vaccination. Chilblain lesions, also known as pernio, are an inflammatory condition usually affecting the acral regions of the body. It is mostly reported from cold and damp areas and has multiple causes associated with it.

Objective: This study aims to review the publicly available data and to provide concise and comprehensive information as well as evaluate the potential pathology, clinical approach, and management of CLL post-vaccination.

Methods: An extensive literature search over PubMed, Cochrane library, Google Scholar, and Clinicaltrials.gov from inception till 5th October 2021, without any restriction of language was carried out. All the recruited articles were reviewed, and their bibliographies were also screened for any relevant information.

Results: 12 studies (10 case reports and 2 case series) were retrieved reporting the incidence of CLL post-vaccination. 8 studies reported incidence in female patients while 5 reported in males, with one study mentioning no gender. Moreover, most of them were either from Europe or the United States of America, except for two cases, reported from Turkey.

Conclusions: Although the overall incidence of Chilblains following COVID-19 vaccination is low, there is still a strong need to find out the exact mechanism behind this to redefine the safety and administration criteria of the vaccines and to formulate a proper management protocol.

Introduction

In December 2019, a zoonotic RNA virus SARS-Cov-2 was isolated in a Chinese patient. The disease caused by it was termed COVID-19 that has spread at an enormous rate throughout the globe [1]. The high infectivity rate and asymptomatic transmission have caused the quick spread leading to a pandemic [2].

The body requires time to respond to the viral attack; hence symptoms usually develop 2 to 14 days post-exposure, typically presenting with fever, cough, dyspnea, fatigue, amnesia, and ageusia [3,4]. In acute conditions, there are incidents of hemoptysis and ground-glass opacities [5]. While SARS-CoV-2 mainly causes respiratory diseases, clinicians have noticed other handful of extrapulmonary manifestations [6,7].

The only way to restore routine life is to speed up the vaccination programs. All the currently available vaccines underwent rigorous trials and were approved after demonstrating an acceptable safety profile[8]. The most common post-vaccination adverse effects are pain at the injection site, fatigue, and chills. However, these effects are transient [9]. However, some severe side-effects have been reported as well including splanchnic venous thrombosis [10] and vaccine-induced immune thrombotic thrombocytopenia [11]. There is a need to address them since reports of adverse events have been regarded as one of the leading motives behind vaccine hesitancy in low- and middle-income countries (LMICs) [12].

One recently reported adverse event attributed to the COVID-19 vaccine is Chilblain or Chilblain-like lesions, illustrated in Figure 1. Chilblain (pernio) is an inflammatory condition, histologically characterized by dermal edema with

perivascular lymphocytic infiltrates, caused by exposure to non-freezing, and cold conditions. It is clinically characterized by bluish-purple papules on acral surfaces, as shown in Figure 2. The causes vary from idiopathic acrosyndrome and Raynaud's phenomenon to systemic diseases such as autoimmune disorders, and rarely in Epstein-Barr virus (EBV) [13–15].

Objectives

This study aims to review the publicly available data and to provide concise and comprehensive information as well as evaluate the potential pathology, clinical approach, and management of CLL post-vaccination.

Methods

Here, we scrutinize the association between coronavirus vaccines and post-vaccination CLL by performing an extensive literature search over PubMed, Cochrane library, Google Scholar, and Clinicaltrials.gov from inception till 5th October 2021, without any restriction of language. To achieve comprehensive results, the keywords used in the search string included “SARS-CoV-2 Vaccine”, “Coronavirus Vaccine”, “Corona Vaccine”, “COVID-19 Vaccine”, “COVID Toes”, “Chilblain”, “Pernio”, “Blue toes”. The terms were separated by BOOLEAN operators “OR” and “AND”. All the recruited articles were reviewed, and their bibliographies were also screened for any relevant information. Ultimately, 12 studies (10 case reports and 2 case series) were retrieved, tabulated in Table 1. This review evaluates the potential pathology, clinical approach, and management of CLL post-vaccination.



Figure 1. Chilblain-like lesions post vaccination. (A) Purpuric patches on the marginal side of fingers [17] (B) Non-painful violaceous lesions on the big toe, the third toe and the fourth toe [78].



Figure 2. Chilblain-like lesions appearance. (A) Characteristic appearance on ventral aspect of feet. (B) close-up of CLL on ventral aspect of feet.

Results

Epidemiology

Most of the cases included in this review reported incidence in female patients, hammering the previously mentioned fact that they have a connection with XX gender [16]. Moreover, most of them were either from Europe or the USA, except for two from Turkey [17]. While there is still a long way to predict the reason behind one region reporting more cases than the other, it highlights potential pathophysiology, i.e., cold environment. Moreover, Cribier B et al. reported a high prevalence of these lesions in cold countries, hence, in affirmation with the cases' findings [18]. The location of included cases is mapped in Figure 3.

Pathophysiology

Chilblain is a superficial and localized inflammatory condition usually occurring in acral regions, especially the toes and fingers, and presents as multiple erythematous edematous papules. It occurs mostly in females and primarily is an abnormal vascular response to nonfreezing cold conditions. It is usually an idiopathic and acute condition. The lesions are associated with tenderness and burning. In severe cases, ulceration, and scars may occur. These lesions may develop as a secondary disorder to connective tissue disease, blood hyper-viscosity, and genetic diseases.

The association between CLL and COVID-19 vaccine is ambiguous. Various potential explanations have been proposed. Some studies mentioned the indirect effect of angiotensin and interferon [19], while other studies mentioned positive immunohistochemistry using monoclonal antibodies against the viral spike proteins and the presence of coronavirus-like particles. It is assumed that the immune response to vaccine or the spike proteins is responsible for this condition [20].

It is established that the Angiotensin-converting enzyme2 (ACE2) serves as a cell receptor mediating the entry of SARS-CoV-2 with the help of transmembrane protease serine 2 (TMPRSS2). This process downregulates ACE2 in cells since it is removed from the external membrane site [21]. Although it allows the entry of the virus into the cell, ACE2 also provides a vaso-protective function by converting Angiotensin II to Angiotensin (1-7). High levels of Angiotensin II lead to endothelial dysfunction and results in vasoconstriction and activation of immune cells and cytokines [22]. It is hypothesized that binding of coronavirus spike proteins leads to shedding and loss of protective function of ACE2 receptor, since Angiotensin (1-7) cannot be formed, and leads to accumulation of Angiotensin II at the tissue level [23]. Similarly, we hypothesize that the spike proteins produced by mRNA (Moderna and Pfizer) and adenovirus vaccines (AstraZeneca) leads to the accumulation of Angiotensin II, by inhibiting the action of ACE2, leading to endovascular damage.

Another proposed mechanism for CLL post-vaccination is the excess of interferons. The way mRNA vaccines may trigger CLL is by increasing interferon-alpha. Upon entry into the cell, the ssRNA and dsRNA are recognized in the cytosol by endosomes and then take part in the innate immune response. Endosomal Toll-like Receptors (TLR) bind to ssRNA in the endosome, while the components of inflammasome bind to ssRNA and dsRNA in the cytosol resulting in INF-1 production alongside multiple inflammatory mediators [24,25]. Although mRNA vaccines are encoded with nucleotides to reduce binding to TLR and reduce high levels of interferon, there might be some unknown pathology, responsible for excessive production of INF-1.

Similarly, the adenovirus vaccine once injected causes innate immunity activation by stimulating macrophages. It engages multiple pattern-recognition receptors, especially TLR9, to induce INF-1 production [25].

Table 1. Case reports and series with characteristic findings.

Author	Age, Sex	Country	Vaccine Administered	Previous Medical History	Presenting Complaint	Days from vaccination to onset of symptoms	Significant examinations and Investigations finding	Treatment	Outcome
Davido et al [78]	41, F	France	Pfizer-BioNTech-162b2	Bipolar disorder, for which she was taking valproate for >10 years.	Sudden toe pain with walking impairment and itching at night, chilblain-like skin	4 days after first dose	Physical examination revealed non-tender, violaceous toes of the left foot. WBC= 70 mmol/L CRP= 1 mg/L anti-Spike (S) antibodies= 0.642 U/ml	Apixaban and low-dose aspirin until circulating immune complexes were obtained <3 µg Eq/ml after 14 day	Recovered after 150 days
Piccolo et al [79]	41, F	Italy	Pfizer-BioNTech-162b2	Not significant	Painful, chilblain-like lesion on the volar aspects of the second and the third fingertip of right hand	24 hours after second dose	High levels of IgG anti-spike antibodies, determining the positive response to the vaccine.	Oral cinnarizine (7.5 mg twice per day)	Recovered after one month
Cameli et al [20]	60, N/A	Italy	Pfizer-BioNTech-162b2	Not significant	Pernio-like lesions on both hands, accompanied by itching and burning sensation	14 days after second dose	Physical examination showed erythematous-violaceous patches and swelling on the fingers. Occasional appearance of livedo reticularis-like manifestations on the lower limbs.	N/A	N/A
Lesort et al [30]	82, F	France	Pfizer-BioNTech-162b2	History of psoriasis and has been on methotrexate for > 10 years	Slightly painful lesions on both hands and feet	24 hours after first dose	Physical examination revealed macular violaceous and erythematous lesions of the fingers and toes.	Topical clobetasol cream, second vaccine dose, she developed chilblain-like lesions again after second dose that were treated similarly.	Recovered

Author	Age, Sex	Country	Vaccine Administered	Previous Medical History	Presenting Complaint	Days from vaccination to onset of symptoms	Significant examination and investigations finding	Treatment	Outcome
Holmes et al [31]	48, F	USA	Moderna	Allergic contact dermatitis to fragrances and positive antinuclear antibodies without rheumatologic disease manifestations	Subtle chilblains-like papules overlying the joint spaces of the hands and feet, tender at palpation.	10 days after the first dose	initial dermatology evaluation suggested hypernasality reaction after which biopsy was recommended.	Patient was taking topical hydrocortisone when she presented, which was continued as it seemed effective.	Recovered after 23 days post vaccination
Meara et al [32]	33, F	USA	Moderna	Mild persistent asthma, hence, a regular user of inhaled corticosteroid	Painful new-onset blue and purple nodules on the tips of 3 fingers and 2 toes	1 week after her first dose	Normal blood work with negative inflammatory markers and autoimmune serologies.	Corticosteroids	Recovered
Lopez et al [33]	64, M	USA	Pfizer-BioNTech-162b2	Not significant	Violaceous skin discoloration for 10 days that started on the left hallux and gradually spread to all toes on the bilateral feet.	3 days after second dose	Laboratory workup was unrevealing	Clobetasol 0.05% ointment for the affected toes with a plan to follow-up in the outpatient dermatology clinic in 2 weeks	Recovered
Pileri et al [80]	42, M	Italy	Pfizer-BioNTech-162b2	Not significant	Nonpainful erythematous-to-purplish patches located on his distal phalanges and nail bed, along with an acrocyanosis of the hands	12 days after first dose	Antibodies and blood tests were negative	N/A	N/A
Temiz et al [17]	44, M	Turkey	CoronaVac	Not significant	Chilblain-like lesions on the dorsal hands	7 days after the vaccine	Dermatological examination revealed mildly pruritic, edematous violaceous plaques and nodules on the dorsal hands	Topical corticosteroids and antihistamines	Recovered
Temiz et al [17]	53, M	Turkey	CoronaVac	Not significant	Chilblain-like lesions on the dorsal hands	7 days after the vaccine	Erythematous-to-violaceous patches on the marginal side of the fingers of both hands-on examination	Topical corticosteroids and antihistamines	Recovered

Table 1 continues

Author	Age, Sex	Country	Vaccine Administered	Previous Medical History	Presenting Complaint	Days from vaccination to onset of symptoms	Significant examination and investigations finding	Treatment	Outcome
Connie Kha, MD et al [34]	70, F	USA	Moderna	Pityriasis lichenoides chronica (PLC), which remained clinically stable with clobetasol 0.05% ointment	Pruritic papular rash on the digits of her right hand. Associated symptoms were pain with movement of the right proximal interphalangeal joints of the 4th and 5th digits that resolved on 10 th day.	2 days after first dose	Physical examination revealed a few lesions located on the extensor surfaces of the extremities. A complete blood count, erythrocyte sedimentation rate, C-reactive protein, rheumatoid factor, Sjogren antibodies (anti-SS-A/anti-SS-B), and antinuclear antibody were either within normal limits or negative.	Clobetasol 0.05% ointment twice daily.	Recovered, however got the same rash 3 days after second dose.
Nebreda et al [81]	N/A, F	Spain	Moderna	Not significant	Itchy edematous erythematous papules on the back of the hands and fingers and erythematous spots in palms	N/A	Superficial perivascular lymphocytic infiltrates with vascular damage and red cell extravasation, with Papillary dermal oedema	Topical corticosteroids and lesions	Recovered
Nebreda et al [81]	N/A, F	Spain	Moderna	Not significant	Itchy edematous erythematous lesions in fingers	N/A	Deep perivascular lymphocytic infiltrates surrounding the sweat glands. Papillary dermal oedema was also present	Topical corticosteroids and lesions	Recovered
Nebreda et al [81]	N/A, M	Spain	Moderna	Not significant	Itchy edematous erythematous lesions in fingers	N/A	Superficial perivascular lymphocytic infiltrates	Topical corticosteroids and lesions	Recovered

CBLL = chilblain-like lesions; CRP = C-reactive protein; F = female; M = male; N/A = Not available; USA = United States of America; WBC = white blood count.

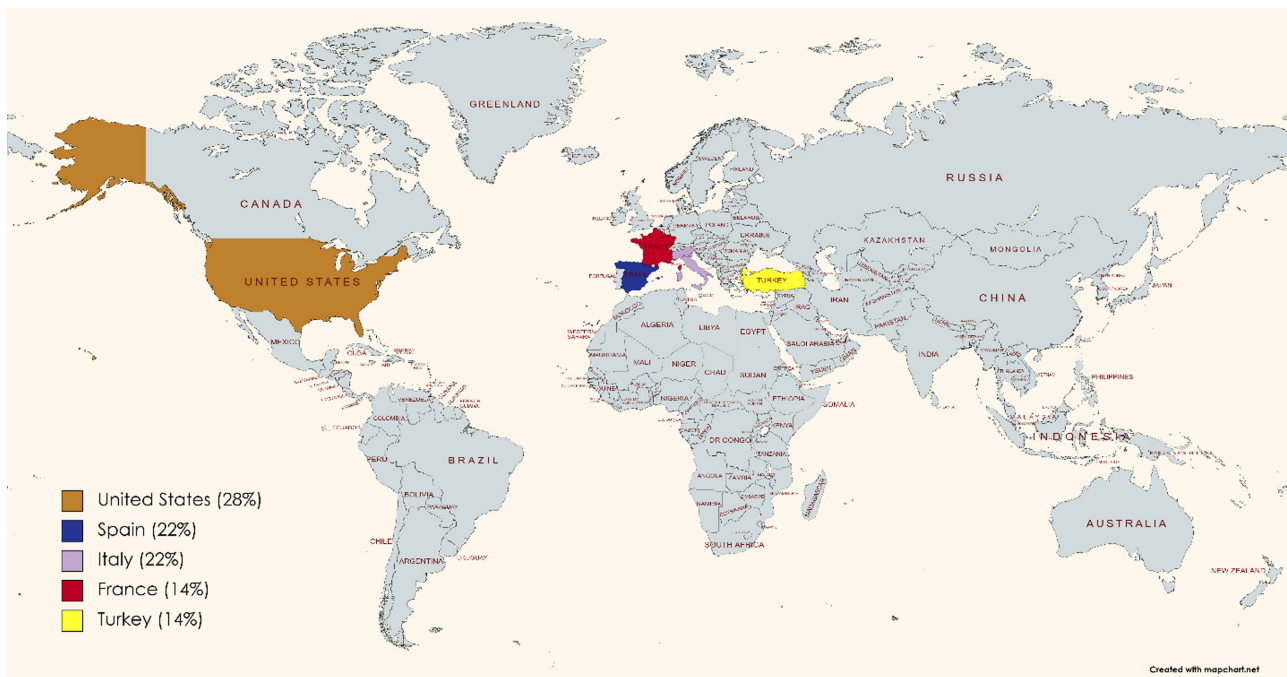


Figure 3. Epidemiology of included cases.

The type 1 interferon is crucial for the host anti-viral response. It leads to activation of the Janus kinase/signal Transducers and Activators of transcription (JAK-STAT pathway) to prevent viral replication. Note that the early and exaggerated response to INF-1 before the humoral activity is considered responsible for the lesions [19,26]. In contrast, the delayed response may lead to hyper-cytokinemias [26].

Another cause of these lesions could be the excessive production of pro-inflammatory proteins. Although there is insufficient evidence of cytokine storm post COVID-19 vaccination in humans, a recent article regarding it in monkeys has raised concerns [27]. It is also documented that some vaccines can activate the myeloid immune system, which can then cause cytokine storm [28]. There is an increase in IL-6, IL-1, TNF- α , and interferon. This causes the influx of macrophages, and neutrophils from the blood into the damaged site. These cells damage endothelial cells, and capillaries. In severe cases, multi-organ failure and death may occur [29].

While there are multiple explanations for CLL post-vaccination, the exact mechanism is still unknown, leaving behind room for future studies.

Histopathology

The use of biopsy to diagnose pernio has been long debated. Despite that it helps in revealing the extent of damage, differentiating the types with it is controversial. Moreover, the pain on the incision is one major concern explaining the hesitancy of its use as a primary diagnostic tool. This may be the potential explanation that only five of the included cases in this review opted for biopsies [30–34].

The common histological finding in the included cases was perivascular lymphocytic infiltrate. This finding is in line with that of Boada et al.[35], where Idiopathic Pernio had 89% of cases having the same histopathology. In Connie Kha et al. [34] immunohistochemical demonstrated the presence of CD31 T cells. This hammers up the finding by Cribier et al [18], where they presented how chilblains have predominant T-lymphocytic infiltration, with only a few B cells. Mild superficial edema was also seen in Meara et al [32].

Holmes et al [31] highlighted the case of a patient with the presence of interstitial eosinophils. In the case by Lesort et al [30] blood vessel endothelial cells of the mid dermis were also seen as a prominent structure. This was also seen in a previous study. While working on the histology of COVID-19 associated pernio, Recalcati et al [36] observed 14 cases, that had a prevalent perivascular pattern, and signs of endothelial activation.

Detailed biopsy reports of included studies are summarized in Table 2. While there exists, much research describing the histopathological finding in different types of chilblains, the ones occurring after COVID-19 vaccination is still unclear. Hence, leaving room for potential working. Figure 4 shows how CLL appears histopathologically in haematoxylin–eosin–safran stain.

Diagnosis

The criterion for CLL diagnosis is unestablished and differs between physicians. Some recommend history and examinations to be sufficient while others prefer going for laboratory testing, including CBC, cold agglutinins, antinuclear antibodies, and cryoglobulins. Some even prefer skin biopsy,

Table 2. Histopathological findings of included cases.

Author	Procedure	Findings
Lesort et al [30]	Skin Biopsy	partly necrotic epidermis overlying a dense dermal lymphocytic infiltrate forming rather well-circumscribed aggregates around blood vessels, eccrine sweat glands and occasionally nerves (Figure 4). The endothelial cells of the blood vessels of the mid dermis were occasionally prominent.
Holmes et al [31]	Skin Biopsy	psoriatic and spongiotic dermatitis with superficial and deep perivascular lymphocyte-predominant inflammation as well as numerous perivascular and interstitial eosinophils. There was no evidence of vasculitis.
Meara et al [32]	Skin Biopsy	Superficial and mid-dermal perivascular cuffed lymphocytic infiltrate. Mild superficial dermal edema is present. No inter-face changes are present. There is no evidence of vasculitis or vasculopathy.
Lopez et al [33]	Punch Biopsy	Superficial and deep infiltrate of lymphocytes around vessels and eccrine glands, with papillary dermal oedema. No thrombi or vasculitis are seen.
Connie Kha et al [34]	Punch Biopsy and Immunohistochemical analysis	Dense and predominantly perivascular lymphocytic infiltrate within the superficial-to-deep reticular dermis. The epidermis appeared normal with no vacuolar changes at the epidermal-dermal junction. There was a notable papillary dermal edema. Within the superficial dermis, some vessels exhibited slightly thickened walls with trophism of lymphocytes, although vascular wall hyalinization, neutrocytosis, or intravascular thrombi were not evident. Immunohistochemical analysis demonstrated a majority of CD3 ⁺ T cells in the lymphocytic infiltrate.

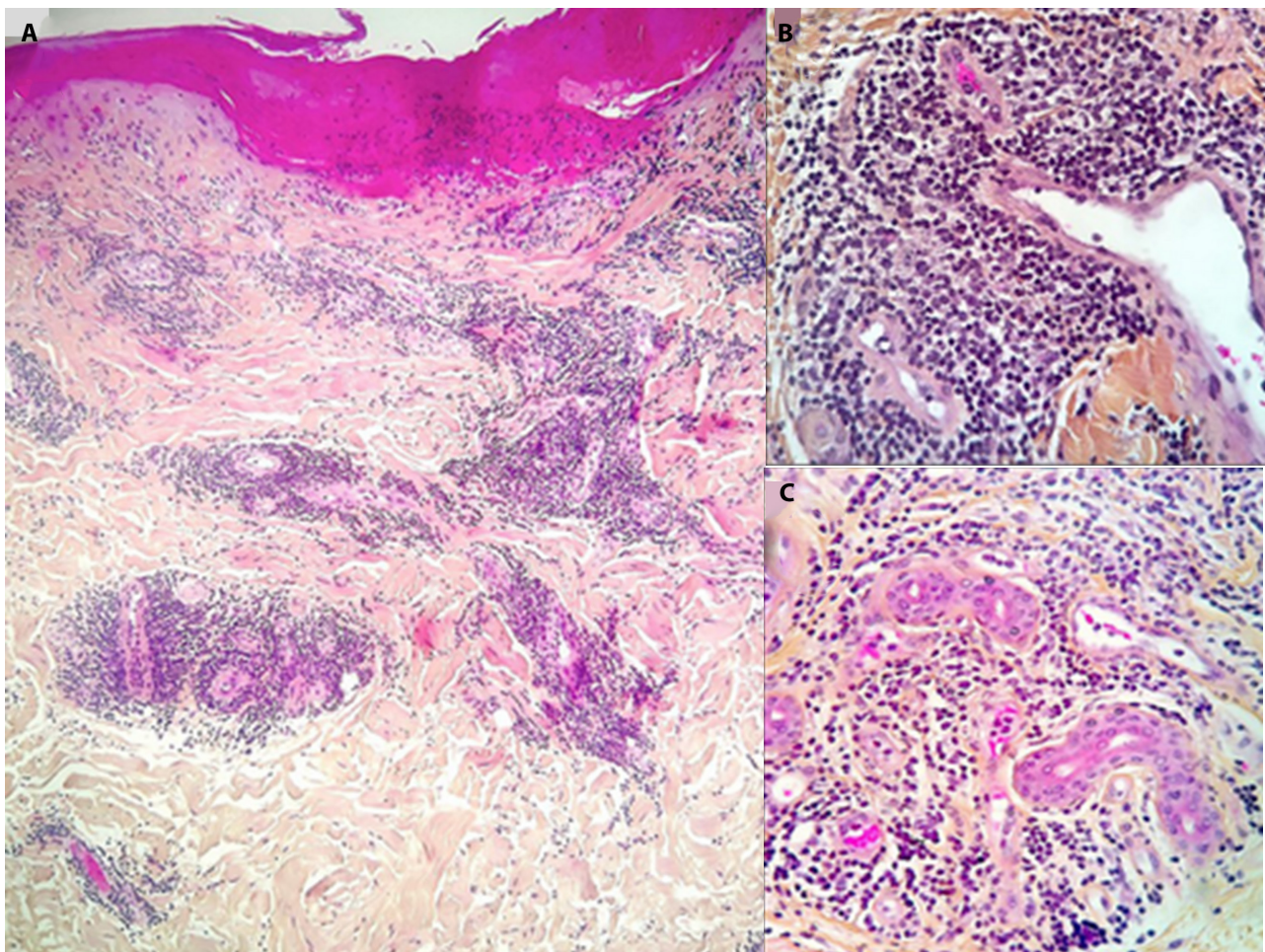


Figure 4. Skin biopsy of the lesion. (A) Necrotic epidermis and a dense dermal lymphocytic infiltrate. (B) aggregation of infiltrates around blood vessels. (C) infiltration around sweat glands (Stain: haematoxylin–eosin–safran stain) [30]

Moreover, one study demonstrated dermoscopy usage to evaluate background vessels and additional features [37].

Cappel et al. studying patients at Mayo Clinic recommend following a systemic approach, starting from history and physical examination to ordering labs and skin biopsy for those with advanced disease [14].

Clinical Management

Some literature suggests no treatment plan for chilblains, as it resolves itself [38]. Whilst some recommend treatment with avoidance of cold and damp conditions. Many studies are determining potential therapeutic measurements in cases of severe disease [15,39]. Pharmacologically, calcium channel blockers, such as nifedipine, are reportedly helpful in relieving the condition [16,40-42].

Herein, we summarize and present a systematic approach to a patient with such lesions based on the current data and treatment plans that worked for patients presented in Table 1.

Exposure

Previously, these lesions were supposed to be caused and aggravated by a cold environment [15,43]. Even though the etiology in post-COVID-19 vaccine CLL is not linked to the weather, physicians, dealing with such cases, may consider the environment as an aggravating factor, as depicted in the cases from colder countries, hence preventing cold weather shall be chosen as a first-line management plan. Moreover, adding on heat provision may also improve symptoms drastically, as proposed by Nyssen et al [15].

Corticosteroids

Topical corticosteroids remained the choice of management in four cases [17,31-33]. However, despite widespread usage, the level of clinical evidence suggesting it is a possible treatment measure is insufficient [39,44]. Souwer et al compared the efficacy of topical betamethasone vs placebo to treat chilblains and no significant differences were perceived [44]. However, Mayo Clinic demonstrated their efficacy, benefiting 6 of 8 patients [14]. This supports the treatment plan followed in included cases. Nevertheless, the contradiction in trial results and actual benefits received by the patients requires a thorough and strong evaluation. Moreover, the cases lack reporting of adverse effects that may have occurred as a result of steroids, hence clinical work in this aspect is crucial.

Calcium Channel Blockers

Calcium channels induce the inhibition of calcium entry into the cells, hence playing a vital role in vasodilation. Since vasospasm due to cold is one of the presumed pathophysiology for chilblains, calcium channel blockers have been

long debated for their efficacy in CLL. Numerous trials and works have been done in this area. Of them all, Nifedipine has been widely recognized, with trials comparing its effect with placebo [45], diltiazem [46], topical 5% minoxidil [47,48], and topical glyceryl trinitrate [49], proving its superiority to them. However, it is still a conflicting treatment option as Souwer et al showed that there was no difference in results in placebo versus nifedipine [50].

In the case of chilblains following COVID-19 vaccination, none of the case reports included in this review (Table 1) used it as a treatment regimen, the plausible reason being the etiology was considered different. However, medicines, that increase blood flow to affected organs have been recommended and used in CLL following COVID-19 infection [38]. Hence, this may highlight the fact that calcium channel blockers can play an important role in vaccine-induced lesions as well. Nevertheless, strong research data are required to connect the dots.

Topical Nitroglycerin

This drug, having the same effects as that of calcium channel blockers, acts by releasing free radical NO, hence relaxing smooth muscles and increasing the blood flow [51].

Topical nitroglycerine (0.2%) showed improvement in outcomes of Chilblains in a study by Verma P et al [52]. Moreover, a case report by Weingarten et al [53], used it as a treatment option for COVID-19 induced CLL and found it effective. However, the first study tested a small sample group (22 patients), while the case only used it for one patient, hence, more work on a greater sample size can be done in the area to weigh the efficacy of this option.

Pentoxifylline

This drug works by improving the red blood cell flexibility by increasing erythrocyte ATP and cyclic nucleotide levels. Current evidence goes in the favor of this option [54]. In the trial by Noaimi, 55% of patients showed improvement in symptoms when treated with pentoxifylline compared to only 27.2% in the group taking prednisolone 0.5mg/kg and topical clobetasol ointment [55]. Another research by Al-Sudany NK et al showed a significant improvement in lesion healing compared with placebo [56]. Moreover, Assimakopoulos et al proposed how this option can be used to resolve other severe complications of COVID-19, highlighting the possible efficacy of this drug [57].

Based on this, pentoxifylline can be considered a part of the treatment plan in patients with CLL.

Hydroxychloroquine

This drug is often used as a first-line treatment in several autoimmune diseases [58]. In a retrospective study by Yang et al, four of five perniosis patients responded well to

Hydroxychloroquine [59]. This can be due to their underlying anti-inflammatory action, which results from their interference with antigen processing in macrophages and other antigen-presenting cells [60].

Acupuncture

In a study by Xiang et al, in 2005, the acupuncture group, combined with massage, showed a 100% effective rate for CLL treatment compared to 76.6% in medicine [61]. Acupuncture is an old Chinese alternative medicine practice, which works by inserting needles into the body, to improve blood flow. While there are reservations to alternative medicine, based on this study, more trials should be performed to verify and to check this therapeutic line of management for CLL.

Temiz et al [17] used antihistamines as a management option, however, there are insufficient data to evaluate their efficacy in CLL; hence, more studies are needed in this regard.

Other cutaneous Manifestations of COVID-19 Vaccines

During the vaccines trial, the typical adverse cutaneous reactions were local injection site reactions while erythema, induration, and tenderness, were specifically reported in Moderna phase III trial [62].

However, as the vaccines entered the real world, diverse cutaneous adverse events have been documented. Mazzatenta et al [63], reported case series, comprising three cases of purpuric eyelid lesions following the Pfizer vaccine, which may be a manifestation of vaccine-induced microangiopathy. Similarly, in another case, the patient experienced urticarial rash along with a flare-up of his previously well-controlled atopic dermatitis [64]. Morbilliform rashes [65,66], urticaria [67,68], pityriasis rosea [68,69], lichen planus [70], and many other cutaneous reactions following COVID-19 vaccination are present in the literature. Notable is the fact that women comprised the majority, which may help draw a relation between any sex-linked reactions. Nevertheless, a thorough evaluation is the need of time to establish complete links [17].

Chilblains like Lesions Following COVID-19 Infection

While COVID-19 vaccines may induce Chilblain-like lesions, similar lesions have been witnessed in mildly infected coronavirus patients as well. The current literature reports numerous cases of COVID-19 infection-associated chilblains [15,71]. In a study by Casas et al [71] involving 375 COVID-19 patients, 19% of cutaneous reactions were manifested as CLL. The authors highlighted the occurrence was more prevalent in younger patients [71].

Piccolo V et al [72] in their research noted that feet alone were mostly affected (85.7%) while those having both feet or hands affected together, and hands alone contributed only 7% and 6% respectively. Similar evidence was observed in the study by Recalcati et al [73] whereof 14 described cases, two cases had both extremity involvement, eight had feet while only four had hands involvement.

However, the major concern is many patients reported, was that they had negative PCR results. Research postulates several theories behind it [13]. One of them specified the relatively late CLL lesion appearance in COVID-19, during the convalescent phase, by which the viral products are no longer detectable on PCR [13,74]. Another clue to pathophysiology has been postulated by considering CLL as a cutaneous expression of a type 1 interferon (IFN-1) response. This may lead to viral product clearance before immunoglobulin production, manifesting as failed serological detection [75,76]. An escalated interferon score was observed in 40% of patients in the study by Lesort et al [77]. Hence, we may hypothesize that high IFN response benefitted the patients, reducing viral replication and defining why the patients were asymptomatic.

Conclusions

There are several limitations in the study highlighting which can lead to a specific conclusion in the future. Firstly, the studies included in this review are limited. Studies with larger sample sizes are required to draw associations between chilblain-like lesions and COVID vaccination. Secondly, the treatment regimen reported in the cases differs drastically with no background reasoning for the choices. Thirdly, one of the included study, Nebreda et al did not specify patients age. More importantly, the cases did not report the side effects of the medications, which is crucial in determining the future of the treatment. It also would have highlighted if the patient recovered via medicines or the pernio self-resolved. Lastly, Nebreda et al only provided an overview and did not list any specifications for each case. Although the overall incidence of Chilblains following COVID-19 vaccination is low, there is still a strong need to find out the exact mechanism behind this to redefine the safety and administration criteria of the vaccines and to formulate a proper management protocol. Similarly, there is a need to address the association between these chilblain-like lesions with gender and different demographic settings. There is an overwhelming need to address issues related to vaccines and their hesitancy amongst the population to successfully restore normal life.

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