Idiopathic perniosis presenting as acral purpuric lesions: Clustering of cases before COVID-19 pandemic and their comparison with chilblain like lesions reported in the literature

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Abstract
Perniosis/chilblains are the acral inflammatory skin lesions developing in susceptible individuals as an abnormal reaction to cold. In the absence of a discernible cause, it is labeled as idiopathic perniosis (IP). With the ongoing COVID-19 pandemic, there was an upsurge of reports of chilblain like lesions (CLL) especially in young patients possibly implicated to the SARS-CoV-2 virus. Twelve clinically suspected and histopathologically confirmed cases of IP seen from November 2019 through February 2020 were retrospectively recruited. Clinical, dermoscopic, and histopathological characteristics of these were reviewed and compared with CLL reported in the literature. Mean age of patients was 26.58 ± 15.18 years with an equal male to female ratio. Characteristic histopathology findings were spongiosis (100%), dermal edema (100%), perivascular lymphocytic infiltrate (100%) with peri-eccrine accentuation (66.7%), keratinocyte necrosis (50%), focal basal vacuolar damage (58.3%), and lymphocytic vasculitis (58.3%). Significant dermoscopy findings were variable background color ranging from dull red and violaceous to copper red and brown orange, coiled vessels (44.4%) and orange-red structureless areas (63.9%). Lesions over palms and soles preferentially had white dots/clods and lines (38.9%). There appears no exclusive histopathological as well as dermoscopy features of CLL and IP, yet certain clues can be appreciated. Keratinocyte necrosis and severe dermal edema favors IP, whereas fibrin thrombi with involvement of both superficial and deep dermal vessels favor CLL. Dermoscopically presence of irregular, linear or branching vessels, red/purple dots and clods and gray brown reticule supports CLL while white dots/clods and lines supports IP.

KEYWORDS
chilblain like lesions, Covid toes, COVID-19, dermoscopy, idiopathic perniosis

1 | INTRODUCTION

Perniosis/chilblains are the acral inflammatory skin lesions that develop in susceptible individuals as an abnormal reaction to cold and damp environment. In a proportion of these patients, an underlying abnormality such as poor nutrition, anorexia nervosa, hematological malignancy, chronic infection, or connective tissue disease is identified. In the absence of such predilection, it is labeled as idiopathic perniosis (IP).1,2 The underlying pathogenesis appears to be cold induced vasoconstriction of deep cutaneous arterioles with dilatation of smaller superficial vessels. The same is reflected in the clinical presentation of erythematous to violaceous macules, papules and plaques associated with edema of fingers and toes, at times resulting in blistering and ulceration. During COVID-19 pandemic such acral purpuric lesions preferentially seen in
young patients gained recognition and were labeled as COVID toes or chilblain like lesions (CLL), suggested by some to be specifically associated with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection.\(^3\) Latency between onset of systemic symptoms and CLL as well as low rates of positive COVID-19 nasopharyngeal reverse transcriptase-polymerase chain reaction (RT-PCR) test suggested these to be a late manifestation of SARS-CoV-2 infection.\(^4\) However, their significance and degree of association with COVID-19 remains to be established with certainty. Clustering of true IP in children consequent to lifestyle changes during the lockdown has also been reported.\(^2\) Histopathological characteristics of CLL have been described in limited studies and appear indistinguishable from IP.\(^3,6-12\) We at our tertiary care center in Dehradun (Uttarakhand) saw clustering of cases of IP from November 2019 till February 2020. The minimum temperature in this region during these months remain between 6.8°C and 10.4°C with high humidity favoring development of IP in vulnerable subjects. Since first case of COVID-19 was reported on 30 January 2020 in India and on 16th March in Uttarakhand (Dehradun), these lesions were not SARS-CoV-2 related. In view of limited available literature, we describe the dermoscopic and histopathological characteristics of IP and compared them with CLL reported in literature during COVID-19 pandemic.

2 | MATERIAL AND METHODS

All clinically suspected and histopathologically confirmed cases of IP seen from November 2019 through February 2020 were retrospectively recruited. A history of Raynaud’s phenomenon, arthritis, systemic symptoms, oral ulcers, and antecedent drug intake was extracted from their clinical records. Complete blood count, antinuclear antibody, prothrombin time, and viral serology’s performed for an occult connective tissue disease, coagulopathy, and chronic infections were noted. Patients with a possible secondary cause were excluded and only cases of IP were included. Final analysis was done only for cases where a skin biopsy was performed and dermoscopy images were available. Dermoscopy was performed in these cases as a routine and the diagnosis was predominantly suspected clinically. A total of 12 cases of IP fulfilling the inclusion criteria emerged. Two investigators retrospectively reviewed dermoscopic and histopathological characteristics of these cases. Histopathology changes were categorized as spongiosis (mild: limited to lower one third of epidermis, moderate: involving lower two third of epidermis, severe: involving full thickness of epidermis), keratinocyte necrosis, lymphocytic exocytosis, basal vacuolar damage, dermal edema, perivascular lymphocytic infiltrate (superficial or deep), pericrinar accentuation of the inflammatory infiltrate, lymphocytic vasculitis (endothelial swelling, red blood cell extravasation and inflammation of vessel walls with or without fibrinoid necrosis), and vessel ectasia. The dermoscopy findings were noted as background color, dots and clods, vessels, white lines and orange red structure-less areas. For dermoscopic evaluation three lesions were selected randomly in each patient making a total of 36 lesions. Dermoscopy images were captured with iPhone X (12-megapixel camera; Apple Inc., Cupertino, CA) attached to DermLite DL200 hybrid, 10x magnification (3Gen, San Juan Capistrano, CA). The dermoscopic and histopathological findings were compared with CLL seen in COVID-19 patients reported in literature to find specific differentiating features if any.

3 | RESULTS

Mean age of the patients was 26.58 ± 15.18 years with a median of 21.5 years. There were six men and six women. The mean duration of lesions was 22.08 ± 14.6 days. All the patients presented with red-purple macules, papules and nodules with or without associated swelling of fingers and toes (Figure 1A,B). Pruritus and pain were the primary symptoms. None of them had any systemic symptoms including fever, cough or sore throat. In 50% patients, only hands were involved, in 25% only feet and in another 25% both hands and feet were involved. Blistering and ulceration were seen in two patients.

Epidermal spongiosis and dermal edema were constant findings seen histopathologically in all patients. The intensity of spongiosis

![FIGURE 1](A) Multiple, tender erythematous to purpuric macules over soles. (B) Multiple erythematous plaques over hands associated with swelling of fingers
varied and was moderate in 58.3%, mild in 25% and severe in 16.7% patients. Keratinocyte necrosis was present in 6 (50%) cases and basal vacuolar damage in 7 (58.3%) (Figure 2A,B). Basal vacuolar damage was confluent in 3 (25%) and focal in 4 (33.3%) patients. Perivascular lymphocytic infiltrate was limited to superficial vessels in 4 (33.3%) cases while in 8 (66.7%) it extended to involve deep vessels as well, with perieccrine accentuation (Figure 2C). Lymphocytic vasculitis was evident in 58.3% patients (Figure 2D). None of the biopsies exhibited fibrin thrombi or fibrinoid necrosis (Table 1).

Dermoscopy characteristics as noted in 36 lesions is given in Table 2. Variable background colors ranging from copper red and brown orange to violaceous and dark red were noted with 6 (16.7%) lesions exhibiting a combination of many colors (Figure 3A-D). Brown/black dots and globules were seen in 8 (22.2%), red in 3 (8.3%) and purple in 2 (5.6%) lesions (Figure 3B). Vessels could be appreciated in 50% lesions with predominant vessel type being coiled (44.4%) (Figure 3C). A characteristic finding seen in lesions over palms and sole was white dots/clods (38.9%) and white shiny lines (11.1%). Orange-red structureless areas were visible in 23 (63.9%) lesions (Figure 3D).

4 | DISCUSSION

Acral purpuric lesions indistinguishable clinically from IP have been regarded by some as strongly associated with COVID-19. However, a

![Figure 2](https://example.com/image2.png)

**Figure 2** (A) Confluent basal vacuolar damage with superficial and deep peri-vascular lymphocytic infiltrate with a perieccrine accentuation (H&E, x4). (B) Focal keratinocyte necrosis with prominent dermal edema and basal vacuolar damage associated with superficial peri-vacular lymphocytic infiltrate (H&E, x10). (C) Perivascular and peri-eccrine lymphocytic infiltrate with lymphocytic vasculitis of vessel wall characterized by lymphocytes in wall of the vessel, endothelial swelling, and red blood cell extravasation (H&E, x10). (D) Fluffy edema of vessel wall with perivascular lymphocytic infiltrate and red cell extravasation (H&E, x10)
low frequency of positive COVID-19 RT-PCR in them fails to support their significance. In children, nasopharyngeal swabs might be falsely negative as there is high likelihood of early elimination of the virus due to more active innate immune response. \(^1\) Docampo-Simon et al in their extensive literature search could identify 88 patients of CLL in whom RT-PCR on nasopharyngeal sample was performed. It was positive in only 14.8% and thus they concluded that CLL are not a specific marker of SARS-CoV-2 infection. \(^1\) El-Hachem et al in their 19 patients presenting with CLL, could demonstrate IgA antibodies to S1 domain of spike protein of SARS-CoV-2 in 6 (31.6%). They suggested a strong relationship between CLL and COVID-19. \(^3\) SARS-CoV-2 spike protein was also detected in cytoplasm of cutaneous dermal vessels and eccrine cells on immunohistochemistry (IHC) of a 35-years-old man presenting with acral purpuric macules although his RT-PCR was negative. \(^1\) Demographic profile of patient's with CLL (younger age group), onset of lesions even in warm temperatures and sudden increase in their incidence discriminates them from IP. \(^3\) A postulated delayed immune reaction to viral infection resulting in micro vascular damage and inflammatory cutaneous lesions can explain the underlying pathogenesis of CLL. \(^1\) On the other hand, cold induced vasospasm producing hypoxemia and secondary inflammatory response is a pre-requisite for IP. In the absence of larger prospective studies, it remains to be validated if CLL are specifically related to COVID-19.

Since facility for IHC to detect SARS-CoV-2 antigens in skin biopsies is available at limited places, identification of specific histopathology and dermoscopy changes of IP and CLL to differentiate them appears most pertinent and cost effective. With this aim, we have reported the histopathology and dermoscopy findings in IP in a cluster of patients presenting prior to the COVID-19 pandemic in our region and compared them with those reported for CLL in the literature (Tables 1 and 2).

| S. No | Histopathology characteristic | (present study) n = 12 | El-Hachem et al\(^1\)\(^3\) (n = 18) | Kanitakis et al\(^1\)\(^6\) (n = 17) | Battesti et al\(^1\)\(^7\) (n = 7) | Ko et al\(^1\)\(^8\) (n = 6) | Hebert et al\(^1\)\(^9\) (n = 5) | Rouanet et al\(^1\)\(^10\) (n = 2) | Locatelli et al\(^1\)\(^11\) (n = 1) | Santonja et al\(^1\)\(^12\) (n = 1) |
|-------|-------------------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|
| 1.    | Epidermal spongiosis          |                      |                      |                      |                      |                      |                      |                      |                      |                      |
|       | • Mild                         | 3 (25)               | 3 (25)               | 7 (58.3)             | 2 (16.7)             |                      |                      |                      |                      |                      |
| 2.    | Keratinocyte necrosis         | 6 (50)               | 4 (22.2)             | 7 (41.5)             | 3 (42.8)             |                      |                      |                      |                      |                      |
| 3.    | Lymphocytic exocytosis        | 3 (25)               | 6 (33.3)             | 2 (12)               | 3 (42.8)             |                      |                      |                      |                      |                      |
| 4.    | Basal vacuolar damage         | 7 (58.3)             | 14 (77.7)            | 3 (18)               | 1 (14.3)             | 2 (33.3)             |                      |                      |                      |                      |
| 5.    | Dermal edema                  | 12 (100)             | 12 (66.7)            | 13 (76.5)            | 4 (57.1)             | 2 (33.3)             |                      |                      |                      | 2 (100) Present         |
| 6.    | Perivascular lymphocytic      |                      |                      |                      |                      |                      |                      |                      |                      |                      |
|       | infiltrate                    | 18 (100)             |                      |                      |                      |                      |                      |                      |                      |                      |
|       | • Superficial                 | 6 (33.3)             |                      |                      |                      |                      |                      |                      |                      |                      |
|       | • Superficial and deep        | 6 (66.7)             | 18 (100)             | 8 (47)               | 7 (100)              | 6 (100)              |                      |                      |                      |                      |
| 7.    | Perieccrine lymphocytic       |                      |                      |                      |                      |                      |                      |                      |                      |                      |
|       | infiltrate                    | 8 (66.7)             | 18 (100)             | 8 (47)               | —                   | 1 (16.7)             |                      |                      |                      |                      |
| 8.    | Lymphocytic vasculitis        | 7 (58.3)             | 3 (16.7)             | 5 (71.4)             | —                   | —                   | —                   | —                   | —                   |                     |
| 9.    | Vessel ectasia                | 7 (58.3)             | —                   | —                   | —                   | —                   | —                   | 2 (100)             | —                   | —                   |
| 10.   | RBC extravasation             | 9 (75)               | (88.2)               | 14 (82.5)            | 4 (57.1)             | —                   | —                   | —                   | —                   | Present              |
| 11.   | Endothelial swelling          | 7 (58.3)             | 15 (83.3)            | 11 (65)              | —                   | —                   | —                   | 2 (100)             | No                  | Present              |
| 12.   | Fibrin thrombi                | 0 (00)               | 2 (11.1)             | 3 (18)               | —                   | —                   | —                   | 2 (100)             | No                  | Present              |

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TABLE 1  Histopathology characteristics of idiopathic perniosis (present study) and chilblain like lesions reported in literature during the COVID-19 pandemic
IP (50%) as compared of CLL (22.2%–42.8%). Basal vacuolar damage has been reported in variable proportions in CLL ranging from 14.3% to 100%.6-11 However, in a large histopathological series of 18 CLL cases, it was seen in 77.7%.3 In the present study 58.3% IP patients exhibited variable degree of basal vacuolar damage. Peri-vascular lymphocytic infiltrate is seen as a perpetual finding in both IP and CLL. However, in CLL most have reported both superficial as well as deep dermal involvement with perieccrine accentuation.6-12 In IP, one third of cases had only superficial perivascular involvement without perieccrine accentuation.6-12 In IP, one third of cases had only superficial perivascular involvement without perieccrine accentuation. Thus there is a high probability of acral purpuric macules representing IP if only superficial vascular plexus is involved. However, deep vascular plexus involvement does not exclude IP. Fibrin thrombi in the vessels were not discernible in any of the IP patients. However, fibrin thrombi in superfi- cial capillaries and dermal venules have been reported in CLL.6,16 Though some have considered fibrin thrombi as a specific finding of CLL; however, these have been previously reported in IP as well.6,8,16 One can be more vigilant in their presence especially if in abundance with an advice for COVID-19 testing in select patients. Thrombosis of dermal vessels has been reported to favor systemic perniosis in the past especially with underlying connective tissue disease.1 Attempts to histopathologically differentiate chilblain lupus from IP also have not delineated statistically significant findings in any of them.

Since dermoscopy as a diagnostic tool can be easily used, we described the dermoscopy findings in 36 lesions of IP and also compared them with those reported in the literature for CLL. After thorough literature search, we could identify two studies of dermoscopy in CLL and none in IP.14,17 A variable background color was seen in IP representing the evolution of lesions. In the initial stage, a dull red color represents superficial dermal inflammation and vessel ectasia. As the lesions evolve, the color changes to copper red and violaceous due to associated red cell extravasation and then orange-brown as a result of hemosiderin deposition. In CLL also, a range of similar background color has been reported. A higher proportion of CLL lesions had red/purple/black dots and globules (60%–92.7%) as compared to IP (36.1%).15,17 These represent red cell extravasation and deposition of hemosiderin degradation products. This suggests that higher proportion of CLL had severe vessel wall damage and correlates histopathologically with involvement of both superficial and deep dermal vessel with high propensity of fibrin thrombi in CLL. Vessels were visible dermoscopically in 50% IP and 100% CLL lesions.15 Predominant type was coiled (44.4%) in IP, while it was irregular, linear or branching vessels in CLL (70%).15 Thus vessel type can be a good pointer to differentiate CLL from IP dermoscopically. Videocapillaroscopy of CLL has also shown severe vascular damage compared to IP as is evident from predominant micro-hemorrhages, dilated capillaries and pericapillary edema.3 Another specific finding seen in IP especially with lesions over palms and soles was presence of white dots/clods and lines. These have been metaphorically referred to as crystalline structure in the past.18 These possibly represent collagen disruption due to dermal edema and correspond with more IP patients exhibiting this finding histopathologically in our series. Gray brown reticule reported by Navarro

### TABLE 2 Dermoscopy characteristics of idiopathic perniosis (present study) and chilblain like lesions reported in literature during the COVID-19 pandemic

| S.No | Dermoscopy characteristic | Idiopathic perniosis (present study) n = 36 | Navarro et al1-17 (n = 41) | Piccolo et al1-15 (n = 10) |
|------|---------------------------|---------------------------------|-----------------------------|-----------------------------|
| 1.   | Background color           |                                 |                             |                             |
|      | • Copper red               | 10 (27.8)                       | 0 (00)                      | 6 (60)                      |
|      | • Red                      | 10 (27.8)                       | 18 (40.9)                   | 4 (40)                      |
|      | • Violaceous               | 3 (8.3)                         | 10 (24.4)                   | –                           |
|      | • Brown orange             | 7 (19.4)                        | 11 (26.8)                   | –                           |
|      | • Mixed                    | 6 (16.7)                        | –                           | –                           |
|      | • Gray                     | 0 (00)                          | 2 (4.9)                     | –                           |
| 2.   | Dots and clods             | 13 (36.1)                       | 38 (92.7) (red/purple)      |                             |
|      | • Red                      | 3 (8.3)                         |                             |                             |
|      | • Brown/black              | 8 (22.2)                        |                             | 6 (60)                      |
|      | • Purple                   | 2 (5.6)                         |                             |                             |
| 3.   | Vessels                    | 18 (50)                         | –                           | 10 (100)                    |
|      | • Coiled                   | 16 (44.4)                       |                             | 1 (10)                      |
|      | • Dot                      | 1 (2.8)                         |                             | 3 (20)                      |
|      | • Irregular                | 1 (2.8)                         |                             | 5 (40)                      |
| 4.   | White structure            | 14 (38.9)                       | –                           | –                           |
|      | • Dots/clods               | 14 (38.9)                       |                             |                             |
|      | • Lines                    | 4 (11.1)                        |                             |                             |
| 5.   | Orange-red structureless areas | 23 (63.9)               | –                           | 3 (30)                      |
| 6.   | Gray brown reticule        | –                               | 12 (29.2)                   | –                           |
et al, representing extensive dermal vessel damage, lichenoid infiltrate and pigment incontinence was not appreciated in our patients with IP. A small sample size and absence of an objective assessment for inflammatory infiltrate, keratinocyte necrosis, basal vacuolar damage, and vascular damage are the primary limitations of this study. Further due to the heterogeneous description of the available data, a statistical analysis to identify specific histopathology or dermoscopy findings could not be performed.

To conclude, though there appears no exclusive histopathological as well as dermoscopy features of CLL and IP, yet certain clues can be appreciated. Keratinocyte necrosis and severe dermal edema favors IP and fibrin thrombi with dense superficial and deep dermal perivascular infiltrate favors CLL. Dermoscopically presence of irregular, linear or branching vessels, red/purple dots and globules and gray brown reticule supports CLL while white dots/clods and lines supports IP.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author, upon reasonable request.

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How to cite this article: Jindal R, Chauhan P, Goyal D, Shirazi N. Idiopathic perniosis presenting as acral purpuric lesions: Clustering of cases before COVID-19 pandemic and their comparison with chilblain like lesions reported in the literature. *Dermatologic Therapy*. 2021;34:e14951. https://doi.org/10.1111/dth.14951