Patient characteristics in tardive COVID-19 pseudoperniosis: a case series of 16 patients

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Summary

Background. Acute pseudoperniosis (PP) has a recognized association with COVID-19 and tends to occur without cold precipitation in young, healthy patients, often without a clear history of COVID-19. These lesions usually resolve within 2 weeks and without long-term sequelae. In the early months of 2021, patients with delayed and protracted PP began to emerge. We have called this presentation ‘tardive COVID-19 PP (TCPP)’.

Aim. To consolidate and expand knowledge on TCPP, we describe the clinical characteristics, treatments and outcomes of 16 patients with TCPP who were reviewed by our outpatient dermatology service.

Results. The initial clinical manifestations were erythema, swelling and PP of the fingers in 56.2%, and of the toes in 31.2%, desquamation in 56.2% and acrocyanosis in 12.5%. Ten patients had eventual involvement of all acral sites. The median duration of symptoms was 191 days. Six patients reported close contact with a confirmed or suspected case of COVID-19, but only two had positive COVID-19 tests. Four patients experienced complete or almost complete resolution of symptoms, while the rest remain under active treatment.

Conclusion. Unlike acute PP, TCPP has a protracted and delayed presentation that is typically associated with profound acrocyanosis. Patients with TCPP represent a new phenomenon that is part of the post-COVID-19 syndrome, with risk factors and pathophysiology that are not yet fully understood. Our data indicate that likely predisposing factors for developing TCPP include young age, a preceding history of cold intolerance and an arachnodactyloid phenotype. Anorexia, connective tissue disorders or sickle cell trait may also predispose to TCPP. In addition, low titre antinuclear antibody positivity, the presence of cryoglobulins, or low complement levels may represent further risk factors. Finally, prolonged low temperatures are also likely to be contributing to the symptoms.

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Classic perniosis (chilblains) present as cold-induced, erythematous or violaceous skin lesions typically involving the fingers and/or toes, and is associated with oedema, itching, pain, burning, blisters or ulceration. Acute pseudoperniosis (PP) has a recognized, but initially contentious association with COVID-19, dating from the beginning of the pandemic. Although COVID-19-associated perniosis resembles classic perniosis, it tends to occur in younger, often otherwise healthy patients, sometimes without a clear history of COVID-19 and without cold precipitation.\(^1\)–\(^3\) These lesions usually last 12–15 days and resolve without long-term sequelae.\(^4\),\(^5\) However, in the early months of 2021, patients with delayed and long-lasting tardive manifestations began to emerge.\(^5\) We describe our experience of 16 such cases.

**Report**

We reviewed 16 patients with PP who had attended our outpatient dermatology service between February and June 2021. The median age of presentation was 29.5 years, and there was a male : female ratio of 1 : 2.2.

Based on their background, patients could be divided in three categories.

The first category (\(n = 4\)) comprised patients with known connective tissue disorders (CTDs) such as chilblain lupus (\(n = 2\)), juvenile psoriatic arthritis (\(n = 1\)) or Raynaud phenomenon (RP) with antinuclear antibody (ANA) positivity (\(n = 1\)). The second (\(n = 10\)) consisted of those with primary RP with negative ANA (\(n = 1\)), RP associated with anorexia nervosa (\(n = 1\)), and those with cool peripheries, acrocyanosis or occasional chilblains during the winter months (\(n = 8\)). The third category (\(n = 2\)) comprised those without a background of autoimmune disorders who also denied prior symptoms of cold intolerance.

Most patients (87.5%; \(n = 14\)) developed painful PP associated with digital oedema, cool peripheries and acrocyanosis. The initial clinical manifestations and site of involvement were reported as erythema, swelling and PP of the fingers (56.2%; \(n = 9\)) or toes (31.2%; \(n = 5\)); differing degrees of desquamation (56.2%; \(n = 9\)); and acrocyanosis of the heels or forefeet (12.5%; \(n = 2\)). Ten patients (62.5%) had eventual involvement of all acral sites (Fig. 1a,b).

Nailfold dermoscopy was performed in 12 patients and demonstrated dilated or abnormally shaped capillary loops in seven patients. Most of these patients (5 of 7; 75%) were also found to have positive ANA results with low titre.

![Figure 1](a) Bilateral acrocyanosis and pseudoperniosis associated with notable nail changes; (b) dusky acrocyanotic fingers with pseudoperniosis and desquamation.
A significant number of the patients (n = 12) were also noted to have an arachnodactyloid phenotype, with long, spindly fingers and toes.

Of the 12 patients with no known CTDs, 6 were newly found to have raised autoimmune markers.

Three patients underwent skin biopsies, and all three had findings in keeping with classic perniosis, such as vacuolar interface dermatitis, mild oedema, erythrocyte extravasation in the papillary dermis, and a moderate cuffed perivascular and peri eccrine lymphocytic infiltrate in the superficial and deep dermis. In one patient, dermal vessels displayed endothelial swelling with focal fibrinoid necrosis and areas with fibrin microthrombi.

Only five patients (31.2%) reported having had any other symptoms compatible with COVID-19 and of these, only two had positive results on antibody tests. None of the remaining patients had ever been found positive for COVID-19; however, six patients reported close contact with a confirmed or suspected case of COVID-19. Of the five patients with classic COVID-19 symptoms, four experienced them during the first wave of the epidemic in the UK (December 2019 to April 2020) and one experienced them during the second wave (October 2020 to March 2021). Four of the five patients developed new or worsening PP/acrocyanosis concurrently or within 3 months of their other COVID-19 symptoms and the fifth developed them after a 9-month delay.

At the time of writing, the duration of symptoms across all patients ranged from 79 to 495 days (2.59–16.27 months), with a median of 191 days.

Patients were treated on their individual merits according to our published algorithm. Four patients (25%) experienced complete or almost complete resolution of symptoms, while the rest remain under ongoing review and active treatment.

A detailed breakdown of individual patient characteristics, interventions and outcomes is given in Table 1.

Acral PP, also known as ‘pseudochilblains’, ‘chilblain-like lesions (CLL)’ and ‘COVID toes’, has become a well-recognized acute entity. Initially contentious, several global case series have demonstrated this to be a predominant dermatological manifestation of COVID-19 disease. In contrast to idiopathic or secondary perniosis, acral PP has largely been described in children or young adults with no exposure to cold temperatures and is largely of short duration (up to 3 weeks), with < 10% of patients having lesions lasting > 60 days. It is noteworthy that PP is commonly seen alongside minimal or no COVID-19 symptoms and is usually associated with negative SARS-CoV-2 tests. In biopsies, pseudochilblains have the same histopathological features as idiopathic and CTD-related chilblains.

Clinical features include acral areas of painful, burning or itchy erythema, oedema, vesicles, pustules, or purpura, with a lack of cold exposure necessity being a distinguishing feature from idiopathic or secondary perniosis.

Unlike the above well-described and acute PP, our cohort of patients had a protracted (median duration of symptoms of 191 days) and usually a delayed presentation that was typically associated with profound acrocyanosis. This presentation has been called ‘long COVID-19 PP’, but we prefer and promulgate the term ‘tardive COVID-19 PP (TCPP)’. Patients with TCPP represent a new phenomenon that is part of the post-COVID-19 syndrome, with risk factors and pathophysiology that are not yet fully understood. To our knowledge, our experience represents the largest series of patients with such tardive skin sequelae related to the COVID-19 pandemic yet to be reported.

Our data indicate that likely predisposing factors for developing TCPP include young age, a preceding history of cold intolerance and an arachnodactyloid phenotype. Anorexia, CTDs or sickle cell trait may also predispose to prolonged TCPP. In addition, low-titre ANA positivity, the presence of cryoglobulins or low complement levels may represent further risk factors, even in the absence of any known CTD. The UK experienced very cold weather during winter 2020 and early spring 2021. Prolonged low temperatures are also likely to have contributed to the symptoms that our patients experienced.

Various theories have been proposed for the mechanism that leads to the development of PP.

According to one prevailing notion, higher levels of interferon (IFN)-α are observed in patients with PP compared with other patients with COVID-19. High levels of IFN-α are also seen in type 1 interferonopathies (in which severe chilblains can be a hallmark of disease); they are thought to drive the development of chilblains and also to contribute to the inhibition of viral particles, thus explaining why patients with PP frequently have clinically milder disease and negative COVID-19 tests.

According to another theory, SARS-CoV-2 immunohistochemical positivity in endothelial cells and the presence of coronavirus particles in the cytoplasm of endothelial cells on electron microscopy suggest the SARS-CoV-2 virus as a direct cause of endothelial damage and thrombosis.
# Table 1 Patient details.

| Patient | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 |
|---------|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Patient demographics** | | | | | | | | | | | | | | | | |
| Sex | M | M | F | F | M | F | M | F | M | F | F | F | F | F | F |
| Age, years | 19 | 19 | 19 | 21 | 15 | 33 | 26 | 15 | 26 | 34 | 71 | 71 | 33 | 37 | 37 |
| **Medical history** | | | | | | | | | | | | | | | | |
| Known RP | No | No | No | Possible | Yes | No | No | Possible | Yes | No | Yes | Yes | No | No | No |
| Known CTD | No | No | No | No | Yes (juvenile arthritis) | No | No | No | No | Yes | Yes (SLE) | No | No | No | No |
| Known eating disorder | No | No | No | No | No | Yes | No | No | No | No | No | No | No | No | No |
| Autoimmune serology | Neg | Neg | Pos<sup>a</sup> | No | Pos<sup>b</sup> | Pos<sup>c</sup> | Neg | Pos<sup>d</sup> | Pos<sup>e</sup> | Pos<sup>e</sup> | No | Neg | Pos<sup>e</sup> | Pos<sup>e</sup> | No | No |
| ESR | 2 | 5 | 25 | 28 | 5 | 2 | 2 | 5 | – | 2 | 31 | 65 | 6 | 5 | 10 | – |
| **Clinical features** | | | | | | | | | | | | | | | | |
| Initial site of symptoms | Toes | Heels | Fingers | Fingers | Toes | Fingers | Forefeet | Fingers | Fingers | Fingers | Fingers | Fingers | Fingers | Fingers | Toes | Toes |
| Both hands and both feet affected | Yes | No | Yes | Yes | Yes | No | Yes | No | Yes | Yes | Yes | No | Yes | Yes | Yes | No |
| PP | Yes | No | Yes | Yes | Yes | No | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Acrocyanosis | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Arachnodactyloid phenotype | Yes | No | Yes | Yes | Yes | No | No | No | Yes | No | Yes | Yes | No | Yes | Yes | Yes |
| Nailfold dermoscopy | No | – | No | Yes | Yes | No | – | – | – | Yes | Yes | Yes | Yes | Yes | No | Yes |
| **Relation to COVID-19** | | | | | | | | | | | | | | | | |
| Classic COVID-19 symptoms | No | No | No | No | No | No | Yes | No | No | Yes | Yes | Yes | Yes | No | Yes | No |
| Contact with known or suspected COVID-19 | No | No | No | No | No | No | No | No | No | No | Yes | Yes | Yes | Yes | Yes | No |
| Time from classic COVID-19 symptoms to PP | – | – | – | – | – | – | – | – | – | – | Synchronous | 2 weeks | Synchronous | 3 months | – | 9 months | – |
| COVID-19 antibodies | Neg | Neg | Neg | Neg | Neg | Neg | Not tested | Not tested | Neg | Neg | Pos | Neg | Neg | Neg | Pos | Pos | |
| Treatment | | | | | | | | | | | | | | | | |
| Clotetasol propionate 0.05% (topical) | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Aspirin | 75 mg | 75 mg | – | 75 mg | – | 75 mg | – | 75 mg | – | 75 mg | – | 75 mg | – | 75 mg | – | 75 mg |
| | once daily | once daily | – | once daily | – | once daily | – | once daily | – | once daily | – | once daily | – | once daily | – | once daily |
| Nifedipine (modified release) | 20 mg | 10 mg | – | 10 mg | – | – | 10 mg | – | 10 mg | – | 10 mg | – | 10 mg | – | 10 mg | – |
| | once daily | twice daily | – | twice daily | – | – | once daily | – | once daily | – | once daily | – | once daily | – | once daily | – |
| Sildenafil | – | – | – | – | – | – | – | – | – | – | 25 mg | – | – | – | – | – |
| | – | – | – | – | – | – | – | – | – | – | TDS | – | – | – | – | – | – |

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Our case series highlight the emerging importance of tardive and persistent PP and acrocyanosis as a manifestation of the long-COVID-19 syndrome. We are concerned about the effect of the next cold spell on these patients and hope that recognition of this entity and adoption of early and appropriate management will lead to better outcomes and minimize morbidity.

References

1. Galván Casas C, Catalá 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.

2. Mehta P, Bunker CB, Ciurtin C et al. Chilblain-like acral lesions in long COVID-19: management and implications for understanding microangiopathy. Lancet Infect Dis 2021; 21: 912.

3. McMahon DE, Gallman AE, Hruza GJ et al. Long COVID in the skin: a registry analysis of COVID-19 dermatological duration. Lancet Infect Dis 2021; 21: 313–14.

4. Public Health England Stay at home: guidance for households with possible or confirmed coronavirus (COVID-19) infection. Available at: https://www.gov.uk/government/publications/covid-19-stay-at-home-guidance/stay-at-home-guidance-for-households-with-possible-coronavirus-covid-19-infection-symptoms (accessed 31 May 2021).

5. 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.

6. Mirza FN, Malik AA, Omer SB, Sethi A. Dermatologic manifestations of COVID-19: a comprehensive systematic review. Int J Dermatol 2021; 60: 418–50.

7. Freeman EE, McMahon DE, Lipoff JB et al. The spectrum of COVID-19-associated dermatologic manifestations: an international registry of 716 patients from 31 countries. J Am Acad Dermatol 2020; 83: 1118–29.

8. National Institute for Health and Care Excellence COVID-19 rapid guideline: managing the long-term effects of COVID-19. Available at: https://www.nice.org.uk/guidance/ng188 (accessed 28 June 2021).

9. Hubiche T, Cardot-Leccia N, Le Duff F et al. Clinical, laboratory, and interferon-alpha response characteristics of patients with chilblain-like lesions during the COVID-19 pandemic. JAMA Dermatol 2021; 157: 202–6.

10. 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.