**Episode 193**: Chilblains or other cutaneous manifestations of SARS-CoV-2 infection and vaccination

Dear colleagues,

First, with many thanks again to Patrick Smits, an update slide show on the novel variant B.1.1.529 now officially the “variant of concern Omicron” (VOC o) and a journalist paper in Nature (where they still think it would be named Nu). More questions than answers.

I guess the staff of Penny Moore will spend their WE in the lab to see if sera from vaccinated subjects can at least neutralize this wicked virus in vitro. Exciting!

Let me remind you of Ep 167-10 (in attachment) where a Japanese group predicted in August that only 4 additional mutations in the Delta variant (K417N, N439K, E484K and N501Y) could render the virus resistant to antibodies, induced by two shots of Pfizer. That “quartet” looks pretty close to Omicron with K417N, N440K, E484A and N501Y! Frightening?

The rest of this episode will be dedicated to cutaneous manifestations.

Pdf at

**Ep 193-1**: Hubiche in JAMA Dermatology April 2021 describes 40 consecutive patients with chilblain-like diseases.

**Clinical presentation:**
- First pruritus and pain of the toes (rarely heels and fingers)
- Then pink-to-red papules or plaques that evolved to violaceous purpuric lesions with frequent bullous and necrotic evolution (Figure 1A and B).
- Acrocyanosis (cyanotic extremities) or cold toes reported in 19 cases.
- None had arterial disease, deep venous thrombosis, or pulmonary embolism.

Twenty-four patients (60%) had contact with possible COVID-19 cases, and 11 (27.5%) met the definition for possible COVID-19 within the 6 weeks preceding

The real-time PCR testing was negative in all cases.
SARS-CoV-2 serology was positive in 12 patients (30%)

**Significant increased release of type 1 IFN in blood after in vitro stimulation.**
Ep 193-2: An earlier investigation (Sept 2021) in UCL Belgium on 31 young patients with chilblains, that appeared during the first wave, concluded that these lesions were NOT associated with SARS-CoV-2, because none of the patients were PCR(+) or SARS-CoV-2 Ab (+). The authors conclude: Lifestyle changes associated with community containment and lockdown measures are a possible explanation for these lesions.

Ep 193-3: The latter suggestion is contradicted by Poizeau in Clin Microbiol Infect (Sept 2021). They conducted a case-control study during lockdown, comparing 102 pt with chilblains and healthy controls. The household members were investigated for SARS-CoV-2: 11 % in the cases.

Ep 193-4: Colmenero in Paed. Dermatology (June 2020) shows evidence of lymphocytic infiltration and viral material, associated with endothelial cells of small vessels and epithelial cells of eccrine glands in 7 teenagers, admitted for chilblains April-May and all PCR(-).


Phenotype = cool extremities with pain/swelling followed by red–violaceous discoloration and finally vesiculation of the toes and fingers.

Figure 1. Pandemic-associated pernio presentation and histopathology.
(a) Representative clinical photographs of COVID toes, with red–violaceous discoloration and swelling on multiple distal digits bilaterally
(b) demonstrating dense perivascular and periannexal inflammatory infiltrate; (insert) magnification demonstrating tight inflammation around eccrine structures (outlined).
(c) Staining of eccrine structures (outlined) for ACE2 (green) and nuclei (blue).
This condition of “chilblains” is seen in relatively young people with clinical suspicion of SARS-CoV-2 infection, but most patients are PCR (-) (0-20 % positive) at presentation and many (0-55 %) also remain SARS-CoV-2 antibody negative.

As shown in the Fig c: **ACE-2 is present in eccrine (sweat) glands** of the skin and also in the endothelial cells of microvasculature. The **Spike has been shown to be associated with these structures, but NOT nucleocapsid or viral RNA**, suggesting than only some viral material, but no live virus is there.

This viral spike elicits an inflammatory reaction (Fig 1B, with mainly lymphocytes and plasmacytoid dendritic cells (pDC). **Type 1 interferon** is being produced (as evidenced by the presence of the “interferon-stimulated gene” MxA.

This SARS-CoV-2 condition is reminiscent of skin lesions of familial chilblain lupus and Aicardi Goutières syndrome, which are characterized by IFN-1 excess. (monogenic disorders referred to as type 1 interferonopathies).

**Pandemic-associated pernio augments the knowledge regarding the spectrum of SARS-CoV-2 infection and reinforces the critical importance of IFN-1 signaling in disease outcomes.**

A robust IFN-1 response in patients who remain asymptomatic and antibody negative could suggest a population with intrinsic resistance to severe COVID-19.

**Ep 193-6:** The SARS-CoV-2 associated inflammatory reactions in young people with chilblains and no or mild COVID needs to be distinguished from the “blue toes” in older, severely ill patients. In the latter case, the cause is thrombo-embolism with no evidence of inflammation. See Fig below

The wider spectrum of cutaneous manifestations associated with COVID

**Ep 193-7:** Freeman in J Am Acad Dermat (Oct 2020) describes a range of manifestations in over 700 COVID patients: morbilliform (= like measles) (22%), pernio-like (= chilblain) (18%), urticarial (16%), macular erythema (13%), vesicular (11%), papulosquamous (9.9%), and retiform purpura (6.4%). Pictures in Fig 1 p. 1125.
Importantky **pernio-like lesions** were common in patients with **mild disease**, whereas **retiform purpura** presented exclusively in **ill, hospitalized patients**. Accordingly, patients with papulosqamous, erythema, urticaria or pernio tenden to be young, while those with moribilliform, vesicular or reticular lesions were older.

Ep 193-8: Casa in Br J Dermat (already in April 2020!) provide a slightly different classification, according to increasing age and severity of other COVID symptoms (see Figs on p 4 and Table on p 5): Pseudo-chillblain - Vesicular – Urticarial – Maculopapules - Livedo/necrosis.

**Cutaneous manifestations after mRNA vaccination**

- Most common: delayed large local reactions > local injection site reactions > urticarial eruptions
- Less common reactions pernio/chillblains, cosmetic filler reactions, zoster, herpes simplex flares, and pityriasis rosea-like reactions.

*Severity calculated based on percentage of patients hospitalized for COVID-19

Fig 1. The spectrum of COVID-19 dermatologic manifestations in all patients, with severity of disease calculated based on the percentage of patients with each condition who were hospitalized. ARDS, Acute respiratory distress syndrome.
Interestingly:
- Several of these reactions mimic those associated with COVID
- Three quarter of the subjects had no medical history, no known allergy.
- These are DELAYED reactions (usually after 24 h) and there is NO association with acute anaphylaxis
- The second dose produced a similar reaction in 43 %, but NOT WORSE.
- It seems more common in females and after Moderna

**Ep 193-10:** An example of a 41 yrs old women with no previous Raynaud syndrome who developed sudden toe pain with walking impairment and itching at night, that appeared 4 days after the first injection with the Pfizer-BioNTech-162b2.

![Image of feet with chilblains](image)

*Figure 1. Non-painful violaceous lesions on the big toe, the third toe and the left-side of the fourth toe, compatible with the so-called ‘COVID toes’*

**General Conclusions:**

Although first controversial, it seems that chilblains are associated with SARS-CoV-2, especially in young people. There are clear indications that a strong type 1 IFN response with inflammation towards the virus is involved, after binding to ACE-2 in microvessels and eccrine glands of the skin. This quick and strong type 1 IFN response may also explain why PCR and serology remains negative and respiratory symptoms are absent or mild.

Chilblains in rather healthy youngsters needs to be distinguished from “blue toes” in elderly patients, caused by thrombosis, which is a rather bad sign, as thrombo-embolic events, associated with COVID may be fatal.

Besides chilblains, there is a wide range of other cutaneous manifestations, according to patient age and severity of COVID disease.

With regard to cutaneous reactions on the (mRNA) vaccines:
- Some are common with other vaccine types (e.g. local injection reactions)
- Some (chilblains, urticaria...) resemble those associated with the disease. This suggests that binding of the Spike protein alone can provoke an inflammatory response.

Importantly, in contrast to immediate reactions (such as generalized urticaria within 1 hour) delayed cutaneous reactions are NOT associated with anaphylactic shock, do not necessarily re-appear after an second dose and therefore are NOT a contra-indication for this second dose.

Best wishes,

Guido