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LETTER TO THE EDITOR

Course and outcome of chilblain-like acral lesions during COVID-19 pandemic

To the Editor,

Exposure to Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) with mild COVID-19 disease can be followed by post-COVID cutaneous inflammation with a spectrum ranging from vasculitis to acral chilblain lesions.[1–4] We have shown that chilblain-like lesions are characterized by activation of the type I interferon (IFN) pathway indicated by expression of human myxovirus resistance protein 1 (MXA) and phosphorylated Janus kinase 1 (JAK1) in lesional skin.[5] To further understand the clinical course and pathogenesis of SARS-CoV-2 associated chilblain-like lesions we followed 25 patients presenting to our department with new chilblain lesions during 2 years of the pandemic (2020–2022; Figure 1a).

Eight of these 25 patients had a history of direct SARS-CoV-2 exposure and four patients had positive SARS-CoV-2 N protein antibodies indicating contact with viral proteins (Figure 1d).

Symptoms ranged from mild reddish pale infiltrated to severe bullous, sporadically necrotic skin lesions at feet (17 patients) and hands (five patients) or both (three patients; Figure 2a).

Histopathologic analysis of acute lesions demonstrated a periadnexal and perivascular pattern in combination with a type I interferon signature indicated by expression of MxA (positive for 11/16 tested patients) and STING (positive for 11/12 tested patients; Figure 2b).

ANAs were present in 14/24 patients (48.3%). The percentage of ANA positive individuals among patients was slightly higher as expected in the general population (36%)[6] and, therefore, might indicate an associated systemic autoimmune response. Interestingly, the patients with chilblain

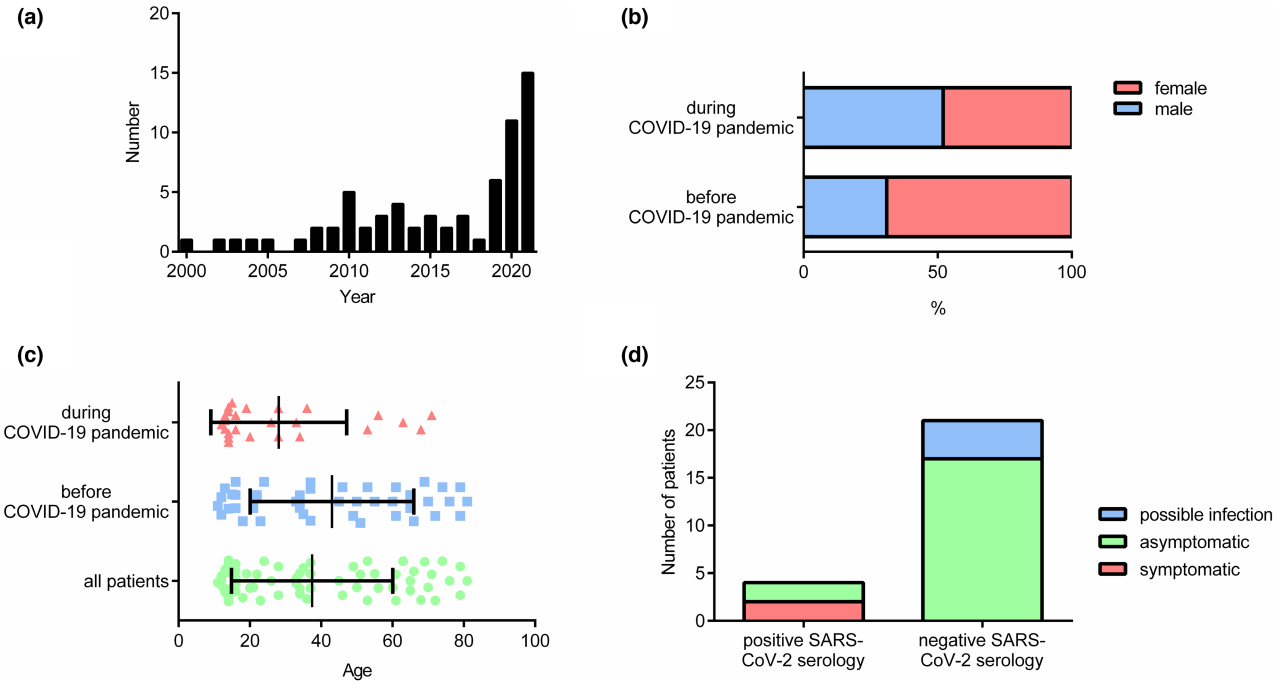

FIGURE 1 (a) Number of patients with the new diagnosis of chilblain lesions presenting to our department from 2000–2022, (b) Gender distribution of all patients ($n = 67$) during and before COVID-19 pandemic, (c) Age at first clinical manifestation of all patients ($n = 67$ patients, green), for patients during COVID-19 pandemic ($n = 25$, red) and before COVID-19 pandemic ($n = 42$, blue); me, mean and SD, (d) Results of SARS-CoV-2 serology in 25 patients with chilblain lesions during the pandemic

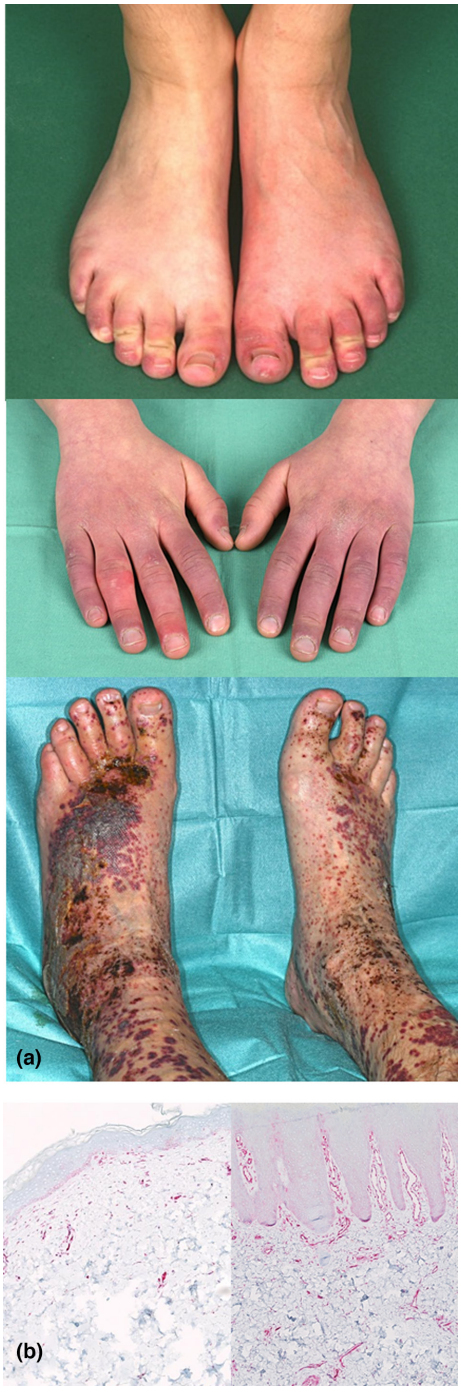

FIGURE 2 (a) Range of clinical symptoms in patients with chilblain lesions and vasculitis post–COVID-19 from mild to severe, (b) The left side demonstrate STING expression in healthy skin (red), the right side shows STING expression in lesional skin of a patient with chilblain-like lesion (haematoxylin-eosin staining, 10×).

lesions diagnosed in the last 2 years were significantly younger (n = 25 patients, mean age 28.1 ± 19.1 years, p = 0.008) than the patients diagnosed before 2020 (n = 42 patients, mean age 43.0 ± 22.9 years) in our department of dermatology (Figure 1c), which might indicate an effect of the pandemic. Alternatively, this difference might be attributed to the fact that older patients did avoid presenting to the doctor because of the higher risk of infection in public. Among the latter, the percentage of male patients was increased (13/25 patients, 52% vs. 13/42 patients, 31%; Figure 1b).

We observed that lesions in most patients (18 out of 25) resolved upon topical treatment with steroids and did not relapse during the observation time of 2–24 months (average time of healing was 7 months). They were, therefore, finally diagnosed with chilblain-like lesions. These observations indicate a mostly benign course of the condition and demonstrate a proficient control of the immune system. McGonagle et al.[7] postulate early disease control by type I IFN restricts viral replication and prevents severe respiratory disease. If this response, however, is not properly ameliorated or causes cellular damage inducing a second flare of type I IFN upregulation, post-COVID manifestation such as chilblain-like lesion can manifest in susceptible individuals.[8]

There might be also a difference in the capacity to induce chilblain lesions among the viral variants. Carmona-Rivera et al.[9] studied multinational cohorts of paediatric and adult patients with COVID-19 and described that patients infected by the omicron variant formed less extracellular neutrophil traps (NETs) compared to other SARS-CoV-2 strains. This correlated with a lower incidence of chilblain-like lesions and might explain the observed decrease in chilblain-like lesions since winter 2022.

Seven patients were diagnosed as chilblain lupus because of an intense periadnexal and perivascular infiltrate in histology, positive ANAs, leukopenia and partly complement deficiency. The total number of patients newly diagnosed with chilblain lupus during these 2 years was not significantly different compared to the number of cases observed in the years before. However, viral infections play an important role as trigger factor in lupus erythematosus[10] and may trigger chilblain lupus. Therefore, we can currently not estimate to which extend the contact to SARS-CoV-2 may contribute to the manifestation of lupus erythematosus in genetically predisposed individuals. Therefore, we recommend a careful medical history and a diagnostic investigation of possible systemic manifestations in all patients with chilblain lesions. The observation of an increased incidence of type I IFN driven chilblain-like lesions in a pandemic setting epidemiologically supports the role of an antiviral immune response for the induction of autoimmune disease.

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CONFLICT OF INTEREST

The authors have no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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