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Complicated coronavirus disease 2019 (COVID-19) in a psoriatic patient treated with ixekizumab

Dear Editor,

At the end of April 2020, a 46-year-old man with type I Brugada syndrome and arterial hypertension reported his history of COVID-19 disease. He had been recently switched to ixekizumab 80 mg following secondary inefficacy of ustekinumab 45 mg for moderate–severe chronic plaque psoriasis. One week after the first dose of ixekizumab, the patient developed fever and malaise. A nasopharyngeal swab resulted positive for SARS-CoV-2. After 4 days from onset of symptoms, he presented to the Emergency Department with dyspnea and chest pain. Oxygen saturation was 90%, and thoracic ultrasound was consistent with bilateral interstitial pneumonia; chest x-ray did not show lung opacities or pleural effusion. The patient was hospitalized and treated with hydroxychloroquine 400 mg BID p.o. the first day followed by 200mg BID, ceftriaxone 1g BID IM, and noninvasive continuous positive airway pressure (CPAP) in courses of prone ventilation. Antivirals were not given because of risk of arrhythmia. Fever remitted after 14 days, enabling transition from CPAP to low-flow oxygen. The patient was discharged after 22 days, with 97% oxygen saturation on walking test. Two repeated SARS-CoV-2 nasopharyngeal swabs resulted negative 30 days from diagnosis.

COVID-19 is caused by the SARS-CoV-2 virus, a new variant beta-coronavirus first isolated from the bronchoalveolar lavage fluid from patients with interstitial pneumonia. On January 30, 2020, the SARS-CoV-2 outbreak was declared a public health emergency of international concern. COVID-19 is characterized most commonly by fever and cough, although the clinical picture may range from completely asymptomatic to bilateral interstitial pneumonia. About 20% of patients develop acute respiratory distress syndrome (ARDS). Risk of severe complications and case fatality rate (CFR) are highest in the elderly, immunosuppressed, and those with chronic diseases.

Uncontrolled immune response and excessive inflammation may play a role in amplifying tissue damage in COVID-19. Levels of interleukin (IL)-1, IL-6, and other proinflammatory cytokines were shown to be significantly higher in patients with severe disease compared to uncomplicated SARS-Cov-2 infection. Increased tumor necrosis factor (TNF) and IL-17 were detected in serum of patients with Middle East Respiratory Syndrome (MERS) caused by coronaviruses and also associated with high morbidity and mortality.[1] It is currently speculated that during the cytokine release syndrome, a frequently fatal clinical sequela of COVID-19 infection, anti-inflammatory drugs may be beneficial.[2] Interestingly, immunosuppressive drugs including tocilizumab, an anti-IL-6 receptor humanized monoclonal antibody, used in rheumatoid arthritis and in controlling the cytokine release syndrome in CAR-T cell therapy, are now under investigation in this context.[2,3] An ongoing clinical trial is evaluating adalimumab, a human anti-TNF monoclonal antibody also used for psoriasis, in severe COVID-19 pneumonia (Chinese Clinical Trial Registry: ChiCTR2000030089).[4] Ixekizumab is a humanized anti-IL-17A monoclonal antibody approved for chronic plaque psoriasis and psoriatic arthritis. Among the most common side effects, upper respiratory tract infections are reported. Since our patient interrupted ixekizumab after its first 160 mg injection, we cannot speculate on its role in COVID-19, although it seems unlikely that it was helpful in preventing a complicated course. Currently, limited data have not yet allowed the implementation of guidelines in predicting the risk of infection and its complications in psoriatic patients treated with biologics. Expert recommendations[5] indicate that their use is relatively safe and that therapeutic decisions should be taken considering the individual patient's characteristics such as age, gender, comorbidities, compliance with safety measures, work-related risks, etc. Arterial hypertension is a common comorbidity of moderate–severe psoriasis, and in our relatively young patient, we did not deem this sufficient to interrupt treatment with ixekizumab for the risk of SARS-CoV-2 infection. Clinical practice should follow currently available data on overall safety profile and licensed indications of ixekizumab before new evidence-based guidelines are definitively issued.

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Chilblain-like lesions during the COVID-19 pandemic: early or late sign?

Dear Editor,

Since the outbreak of novel coronavirus disease 2019 (COVID-19), reports concerning acral cutaneous manifestations are progressively increasing.

We read with interest the article by Landa et al., entitled "Chilblain-like lesions on feet and hands during the COVID-19 Pandemic," published in the *International Journal of Dermatology*.[1]

The authors described a case series of six patients who presented with chilblain-like lesions on the extremities. Of the six cases, three were COVID-19 confirmed by PCR (one patient was tested 3 weeks before cutaneous involvement). Of the six cases, three referred cough, fever, or congestion 3–4 weeks before, while none reported other coronarovirus symptoms at the onset.

In our hospital, we observed several chilblain-like lesions in children and young adults from the beginning of March, concurrently with the pandemic outbreak. We described 14 patients who presented with no systemic symptoms; only in three cases (21%) cough and fever were documented 3 weeks before the onset of the cutaneous lesions. Both nasopharyngeal (n = 3) and rectal swabs (n = 2) for COVID-19 yielded negative results. Skin biopsies were performed in four cases, showing a lymphocytic dermal infiltrate with a prevalent perivascular pattern and signs of endothelial activation. We could not find similar lesions in 107 COVID-19-positive patients (average age 72.2 years) hospitalized in the same period for acute pneumonia. These observations led us to suggest that chilblain-like lesions could be late signs of COVID-19.[2] Interestingly, during the follow-up of the patients, we observed new lesions relapsing after weeks from the onset in three cases, suggesting an ongoing inflammatory process.

Kolivras et al. reported chilblain-like lesions in a COVID-19-positive 23-year-old male.[3] The appearance of the plaques was preceded by low-grade fever for 3 days. A previous history of psoriasis treated with secukinumab until 1 month before was documented. They concluded that chilblains may be early symptoms of COVID-19 and that affected patients are likely contagious.

Recently, Piccolo et al.[4] reported on 63 patients collected through social media. In most cases, systemic symptoms (gastrointestinal and respiratory symptoms, fever) preceded cutaneous findings. COVID-19 status was assessed only in 11 cases, with two positive patients. Serology/PCR for other infections was available in 10 patients. They concluded that the prototype of patient is an otherwise healthy adolescent with occasional history of general symptoms preceding cutaneous lesions.

Little is known so far about etiology and pathogenesis of these acral lesions, and whether they are an early or a late sign is controversial. Both our findings and the case series by Landa et al. and Piccolo et al corroborate the hypothesis that these lesions could be more likely a late manifestation of COVID-19, because they appear usually weeks after systemic symptoms, with mostly negative COVID-19 swab results. The swab negativity could be explained with the disappearance of viral presence detectable at PCR, after a brief, usually asymptomatic course, in young healthy subjects. The perniotic skin lesions could therefore be linked to a delayed immune-mediated response addressing the small cutaneous blood vessels. Thus, children could be facilitators of viral transmission in the early stage, before skin involvement.

In conclusion, the "epidemic" of chilblain-like lesions strongly supports the hypothesis of an infectious etiology of this particular condition. It is essential to rule out other viral