COVID-19 SPECIAL FORUM

Nail changes as manifestation of systemic disease in COVID-19 infection

To the editor

Skin is one of the most commonly affected organs by the SARS-CoV-2 infection. Different manifestations including skin, mucous membranes and hair have been reported.[1] Until recently, not many articles incorporate nail manifestations of COVID-19.[2] We conducted a literature search in Pubmed, Embase, The Cochrane Library, EBSCO and Google scholar databases regarding all the case reports and series of nail changes associated to COVID-19 infection. Included cases are summarized in Table 1.

A total of six case reports were found: two reported beau lines,[3,4] two red half-moon nail sign,[2,5] one onychomadesis[1] and one a distal orange discoloration.[6] Median age was of 53.5 years (range 37 to 89 years). Four patients were females and two males. Median time of onset of nail manifestations after the diagnosis of COVID-19 was of 56 days (range 2 to 112 days). The earliest manifestations were red half-moon nail sign, 2 and 14 days after diagnosis, and the latest the distal orange discoloration. Beau lines appeared after 28 and 98 days and onychomadesis after 84 days. Different COVID-19 symptoms were described, and the most frequently found was fever, which was present in four patients. After this, dyspnoea and cough were reported in three patients each. Other found symptoms were diarrhoea, anosmia, ageusia and sore throat. Of the six included patients, three required hospital admission and in one of these oxygen requirements were reported (red half-moon nail sign). The most commonly used treatment was hydroxychloroquine (3/6) and ceftriaxone (2/6). Other used therapies were methylprednisolone, lopinavir/ritonavir, oseltamivir and heparin.

Nails, like the rest of the skin, could provide important information regarding COVID-19 disease and systemic involvement.[6] The exact pathogenesis of nail changes in patients with SARS-CoV-2 infection has not been completely understood. The red half-moon nail sign, which represents a transversal red band that surrounds the distal margin of the nail´s lunula, could be associated to microvascular injury or to a procoagulant state connected to an inflammatory immune response.[5] Because of the location, the distal subungual arcade´s capillary network might be affected in these cases.[5] Beau lines or transverse grooves in the nail plate can be caused by a temporary interruption of nail matrix growth.[3] In more severe cases, an inhibition of the nail´s proliferation causes a separation of the nail plate from the nail bed with an eventual shedding or onychomadesis.[1] These alterations often occur after a systemic insult, such as infections, critical illnesses, drugs or autoimmune diseases.[1,3] Lastly, no clear explanation for the transverse orange nail lesions has been found, but the shape of the discoloration favours a systemic illness.[6] All of these findings have been previously described in Kawasaki disease, a disease that like COVID-19 has a vascular aetiology.[6]

The published evidence regarding nail changes and COVID-19 is scarce, and no conclusion of the aetiology can be clearly made. We prompt authors to investigate and document nail

Table 1 Summary of published case reports of nail manifestations in patients with COVID-19

Authors	Number of patients	Gender	Age	Nail manifestation	Time of onset (days)	COVID-19 symptoms	Hospital admission	Oxygen requirement	Treatment for COVID-19
Alobaida *et al.* 2020[3]	1	M	45	Beau lines	98	Diarrhoea, fever, and dyspnoea	No	NR	NR
Ide *et al.* 2020[4]	1	M	68	Beau lines and leuconychia	28	Fever, dyspnoea	Yes	NR	HCQ, 6-MP
Méndez-Flores *et al.* 2020[2]	1	F	37	Red half-moon nail sign	2	Anosmia, cough, fever	No	No	NR
Neri *et al.* 2020[5]	1	F	60	Red half-moon nail sign	14	Fever, cough, dyspnoea, anosmia, ageusia	Yes	Yes	HCQ, L/R, ceftriaxone, heparin
Tammaro *et al.* 2021[6]	1	F	89	Orange discoloration	112	Cough, asthenia	NR	NR	NR
Senturk *et al.* 2020[1]	1	F	47	Onychomadesis	84	Sore throat	Yes	NR	HCQ, azithromycin, oseltamivir, ceftriaxone

M, Male; F, female; NR, not reported; HCQ, hydroxychloroquine; 6-MP, methylprednisolone; L/R, lopinavir/ritonavir.

changes in COVID and post-COVID patients in order to obtain a panoramic image of COVID-19′s systemic manifestations. Nails can function as an alarm sign for physicians regarding systemic diseases, including COVID-19.

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Conflicts of Interest

None declared.

S.S. Ocampo-Garza,[1,2] J. Ocampo-Candiani,[1] E. Camela,[2] M. Vastarella,[2] G. Fabbrocini,[2] M. Scalvenzi,[2] A. Villani[2,*]

[1]Departamento de Dermatología, Universidad Autónoma de Nuevo León, Hospital Universitario ¨Dr. José Eleuterio González¨, Monterrey, Nuevo León, México, [2]Dermatology Unit, Department of Clinical Medicine and Surgery, University of Naples Federico II, Naples, Italy

*Correspondence: A. Villani. E-mail: ali.vil@hotmail.it

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Recurrence of previous chilblain lesions during the second wave of COVID-19: can we still doubt the correlation with SARS-CoV-2?

To the editor,

Between March and April 2020, after the onset of the first wave of the COVID-19 pandemic, a cluster of acral chilblain-like lesions (ACBLL) was observed in young subjects.[1,2] Despite efforts to substantiate the correlation of ACBLL with SARS-CoV-2 infection, only a minority of cases have tested positive on reverse transcriptase-polymerase chain reaction (RT-PCR) or serology. Only 3 of the 33 patients with ACBLL seen at our hospital in this period had evidence of recent SARS-CoV-2 infection on these tests. In all cases, skin lesions developed 1-4 weeks after the COVID-19 pandemic peak in the local population and resolved spontaneously within 4–12 weeks after their onset.

Following the start of the second pandemic peak, in the fall of 2020, we observed 7 new cases of ACBLL with clinical and laboratory features similar to those of the cases seen in the first wave. Again, only one of the seven patients tested positive on RT-PCR or serology for SARS-CoV-2. The temporal relationship between this second cluster and the pandemic outbreak was similar to that observed previously.

Importantly, besides the 7 new cases, 6 of the 33 patients seen during the first wave returned to our observation because of the recurrence of ACBLL, which developed 1–4 weeks after the second COVID-19 peak; the clinical features were comparable to those of the previous episode. Three of the six had systemic and/or respiratory symptoms before the relapse of ACBLL. Three reported recent contact with a confirmed case of COVID-19. All patients tested negative for SARS-CoV-2 on RT-PCR. Only one patient, who was already positive for IgG at the first evaluation, had positive IgM and IgG for SARS-CoV-2 (Maglumi, 2019-nCoV IgM and IgG CLIA assays; Snibe diagnostics) at the time of relapse.

Skin biopsy, performed in 5 of the 6 patients with reactivated lesions, showed a non-specific histological picture consistent with published reports of COVID-19-associated ACBLL[3,4] (Fig. 1). Constant features were as follows: cuffed perivascular lymphocytic infiltrate with oedema and variable fibrinoid changes – consistent with lymphocytic vasculitis – in the dermis, often extending into the subcutaneous tissue. A lymphocytic infiltrate around sweat glands was also present in all cases. On immunohistochemistry, the inflammatory infiltrate was mostly composed of CD3+ T lymphocytes (with a normal CD4/CD8 ratio), together with scattered CD20+ B lymphocytes and occasional CD68+ histiocytes. Inconstant features were as follows: dermal oedema, vacuolar interface changes and accumulation of dermal mucin among the collagen fibres of the dermis.

Of note, 6/6 reactivations occurred at the identical anatomical site involved in the first episode, and the pattern, shape and morphology were the same as those of the previously observed lesions (Fig. 2).

Recent dermatoscopic observations and histopathological data of microvascular damage[5,6] argue in favour of our hypothesis that SARS-CoV-2-induced vascular damage could have persisted subclinically after the disappearance of skin lesions, as a consequence of smouldering T-cell-mediated immune response. Further contact with SARS-CoV-2 might have again triggered a local inflammatory response, which, in turn, might have led to the recurrence of full-blown ACBLL.

Our observation of the reactivation of ACBLL during the second COVID-19 wave in patients who had comparable lesions in

