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Evaluation of SARS-CoV-2 antibodies in 24 patients presenting with chilblains-like lesions during the COVID-19 pandemic



To the Editor: Chilblains-like lesions have been reported in primarily young, healthy patients with suspected or confirmed severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) infection^{1,2} and are characterized histopathologically by chilblains-like changes, without necrosis.³ Although SARS-CoV-2 viral particles have been identified within endothelial cells of patients with chilblains-like lesions,⁴ negative results or absent SARS-CoV-2 laboratory testing in other patients has created uncertainty about the relationship between coronavirus disease 2019 (COVID-19) and chilblains-like lesions. We evaluated this relationship by performing multiple tests for SARS-CoV-2 antibodies on patients with chilblains-like lesions during a surge of SARS-CoV-2 infections.

Our dermatology service offered antibody testing to 26 consecutive patients with chilblains-like lesions evaluated during a surge of SARS-CoV-2-infections. Two patients declined participation. Testing was performed on the following platforms: Abbott Architect (IgA, immunoglobulin [Ig] M, IgG, repeat IgG; Abbott, Abbott Park, IL); DiaSorin Liaison (Saluggia, Italy) SARS-CoV-2 S1/S2 (IgG); and Euroimmun SARS CoV-2 enzyme-linked immunosorbent assay (IgG) (Euroimmun US, Mountain Lakes, NJ). Clinical information was obtained via medical record review.

All 24 patients (100%) tested negatively for SARS-CoV-2 IgG on 2 separate tests on the Abbott Architect platform, 21 (87.5%) tested negatively on the Euroimmun IgG platform, and 23 (95.8%) tested negatively on the Liaison Sars-Cov-2 platform (Table 1).

All 24 patients (100%) tested negatively for IgA antibodies, 22 (91.7%) tested negatively for IgM, and

21 (91.67%) completed nasopharyngeal polymerase chain reaction testing for SARS-CoV2. Of these, 20 (95.2%) tested negatively. No patients reported a prior history of chilblains.

We observed minimal evidence of SARS-CoV-2 antibodies in patients identified with chilblains-like lesions because only 4 of 24 patients (16.7%) tested had any positive results and none had multiple positive results.

Despite our findings, an association between chilblains-like lesions and SARS-CoV-2 infections may exist. Our patients may have had SARS-Cov-2 infection but failed to mount a detectable antibody response. Chilblains-like lesions may be associated with mild infections in patients and who test negative on polymerase chain reaction,¹ and patients with mild clinical courses may mount weak antibody responses.⁵ Problems with the timing or accuracy of antibody tests could produce negative results. Our patients were tested an average of 23.65 days from symptom onset, a timing thought to correlate with detectable IgG levels; however, 4 patients reported fewer than 14 days of cutaneous symptoms before testing, which may not have allowed sufficient time to produce antibodies. By testing patients on multiple platforms, we sought to reduce the likelihood of false-negative results. The observed discordance in IgG results in 4 patients suggests individual results may be unreliable.

Inappropriate patient selection through diagnostic error, anchoring bias, or selection bias could have occurred, although we attempted to minimize this by having multiple board-certified dermatologists review each patient's photographs. An epiphenomenon, whereby the COVID-19 pandemic leads to changes in behavior that may predispose patients to chilblains-like lesions without a causal link, is also possible.

In conclusion, we found a low frequency of SARS-CoV-2 antibodies in 24 patients presenting with chilblains-like lesions during a SARS-CoV-2 outbreak and discordance across different testing platforms. Patients presenting with chilblains-like lesions should not be presumed to have serologic immunity to SARS-CoV-2 as a result of recovery from prior infection, without confirmatory testing.

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Table I. Clinical description and SARS-CoV-2 polymerase chain reaction (PCR) and antibody test results of patients with chilblain-like lesions evaluated between April 13 and May 24, 2020

Patient	Sex/ age, y	Lesion location	Symptoms	Dur., d*	Systemic symptoms	SARS-CoV-2 laboratory testing				
						PCR	Antibody test platforms†			
							Abbott (initial)	Abbott (repeat)	Euroimmun	Liaison
1	F/27	B/I dorsal and palmar fingers, toes	Pruritus	60	None	(–)	IgG (–), IgM (e), IgA (–)	IgG (–)	IgG (+)	IgG (–)
2	F/30	B/I dorsal toes	Tenderness	26	Fatigue, sinus congestion	(–)	IgG (–), IgM (–), IgA (–)	IgG (–)	IgG (–)	IgG (–)
3	F/27	B/I dorsal and plantar toes	Tenderness	31	Fatigue, sore throat (EBV viral capsid IgM+)	(–)	IgG (–), IgM (–), IgA (–)	IgG (–)	IgG (–)	IgG (–)
4	M/64	B/I dorsal toes	Discomfort	10	None	(–)	IgG (–), IgM (–), IgA (–)	IgG (–)	IgG (–)	IgG (–)
5	M/26	B/I dorsal toes	Pain, swelling	22	Globus sensation in throat	(–)	IgG (–), IgM (–), IgA (–)	IgG (–)	IgG (–)	IgG (–)
6	M/33	R dorsal toes	Tenderness	20	None	(–)	IgG (–), IgM (–), IgA (–)	IgG (–)	IgG (+)	IgG (–)
7	F/11	R 1st distal toe	NA	25	None	NP	IgG (–), IgM (–), IgA (–)	IgG (–)	IgG (–)	IgG (–)
8	M/12	B/I dorsal toes	Stinging, swelling	32	Lethargy, poor appetite	NP	IgG (–), IgM (–), IgA (–)	IgG (–)	IgG (+)	IgG (–)
9	M/41	B/I dorsal toes	Stinging, tenderness, pruritus	33	Fatigue, sore throat	(–)	IgG (–), IgM (–), IgA (–)	IgG (–)	IgG (–)	IgG (–)
10	F/55	B/I plantar toes	Burning, tenderness	23	None	NP	IgG (–), IgM (–), IgA (–)	IgG (–)	IgG (–)	IgG (–)
11	F/24	B/I dorsal toes	Pain, pins and needles	30	Fever, chills, fatigue, sore throat, cough	(–)	IgG (–), IgM (–), IgA (–)	IgG (–)	IgG (–)	IgG (–)
12	M/31	B/I dorsal and palmar fingers	Soreness, tenderness	28	None	(–)	IgG (–), IgM (–), IgA (–)	IgG (–)	IgG (–)	IgG (–)
13	M/25	B/I dorsal and lateral toes	Tenderness, pruritus	22	Fatigue, sore throat, dry cough, sinus congestion	(+)	IgG (–), IgM (–), IgA (–)	IgG (–)	IgG (–)	IgG (–)
14	M/37	B/I dorsal toes	Pruritus	12	Sore throat, myalgias	(–)	IgG (–), IgM (+), IgA (–)	IgG (–)	IgG (–)	IgG (–)
15	M/31	R dorsal and plantar toes	Tenderness	24	Fatigue, headaches	(–)	IgG (–), IgM (–), IgA (–)	IgG (–)	IgG (–)	IgG (–)
16	F/19	B/I dorsal toes	Pain	14	None	(–)	IgG (–), IgM (–), IgA (–)	IgG (–)	IgG (–)	IgG (–)
17	F/28	R dorsal toes	NA	21	Sore throat, rhinorrhea	(–)	IgG (–), IgM (–), IgA (–)	IgG (–)	IgG (–)	IgG (–)
18	M/59	B/I dorsal and plantar toes	None	NA	None	(–)	IgG (–), IgM (–), IgA (–)	NP	NP	NP
19	M/28	B/I dorsal toes	Pruritus	21	Chills	(–)	IgG (–), IgM (–), IgA (–)	IgG (–)	IgG (–)	IgG (–)
20	F/33	R dorsal toes	Pain, tenderness, pruritus, swelling	31	Papular rash on chest and axillary fold	(–)	IgG (–), IgM (–), IgA (–)	IgG (–)	IgG (–)	IgG (–)
21	F/31	R dorsal toes	Pruritus	21	Sore throat, diarrhea	(–)	IgG (–), IgM (–), IgA (–)	IgG (–)	IgG (–)	IgG (–)
22	F/32	R 2nd palmar finger	Tenderness, pruritus	22	Sinus congestion	(–)	IgG (–), IgM (–), IgA (–)	IgG (–)	IgG (–)	IgG (lp)
23	M/25	L dorsal toes	Pain, pruritus	8	Cough, shortness of breath, rhinorrhea; sore throat	(–)	IgG (–), IgM (–), IgA (–)	IgG (–)	IgG (–)	IgG (–)
24	F/41	R plantar toes	Pain	8	None	(–)	IgG (–), IgM (–), IgA (–)	IgG (–)	IgG (–)	IgG (–)

B/I, Bilateral; Dur., duration; EBV, Epstein-Barr virus; F, female; IgG (lp), IgG low positive; IgM (e), IgM equivocal result; L, left; M, male; NA, data not available; NP, test not performed; R, right; –, negative test result; +, positive test result.

*Duration from reported onset of pernio symptoms to time of SARS-CoV-2 serology laboratory draw.

†Abbott Architect, Abbott, Abbott Park, Illinois; DiaSorin Liaison, Saluggia, Italy; Euroimmun US, Mountain Lakes, New Jersey.

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Skin is a potential host of SARS-CoV-2: A clinical, single-cell transcriptome- profiling and histologic study



To the Editor: The novel coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread worldwide. The lung is the main target organ of SARS-CoV-2; however, extrapulmonary virus distribution¹ has been observed. Skin manifestations, including skin rashes, morbilliform exanthema and chilblains,²⁻⁴ have recently been reported as possible presentations in patients with COVID-19. However, the number of such cases has been relatively small, and whether SARS-CoV-2 might infect injured skin and cause COVID-19 is still unknown. We therefore examined whether the skin is a potential host of SARS-CoV-2 by analyzing clinical, histologic, and single-cell transcriptome data.

This retrospective analysis included 3128 patients with laboratory-confirmed COVID-19. Data were collected from the Shanghai Public Health Clinical Center and Wuhan Leishenshan Hospital. Skin rashes were present in 52 patients (1.66%). Among them,

obvious skin lesions were present in 17 patients (0.54%) before the other symptoms of COVID-19 and in 35 (1.12%) in the early stages of the COVID-19 infection (Fig 1, A and Supplemental Table I, available via Mendeley at <https://data.mendeley.com/datasets/scvph5w5jr/1>). The skin rashes were urticarial in 52 patients (52%), followed by papules (15%), erythema and papules (14%), scratch (10%), rhagades (6%), and chilblains (4%).

Among the 52 patients with skin rashes, 21 patients were treated with oral corticosteroid (prednisone, 10 mg thrice daily), and the average time for skin rash recovery was 4.2 ± 2.3 days. This was significantly shorter than 8.3 ± 5.1 days in patients who were not treated with corticosteroid (Supplemental Table II). Although the use of corticosteroids in treatment of patients with COVID-19 remains controversial,⁵ our data suggested that skin lesions are associated with COVID-19 and that corticosteroid therapy is effective.

To further investigate the association of SARS-CoV-2 and skin rashes present in patients with COVID-19, we performed single-cell RNA sequencing with keratinocytes from normal human skin. The data showed that angiotensin-converting enzyme 2, the viral host cellular receptor, was highly and specifically expressed in the granulosum of the skin, whereas transmembrane serine proteases were relatively scattered in all keratinocytes and melanocytes, and in duct, Schwann, and neurocyte cells. The coexpression of angiotensin-converting enzyme 2 and transmembrane serine proteases was particularly found in the granulosum (Fig 1, B). Nucleocapsid protein was expressed in cytoplasm of epidermis from patients with COVID-19 but was not detected in normal skin tissue (Fig 1, C). These data suggested that the skin is a potential host of SARS-CoV-2. Although this hypothesis needs further study, it is intriguing to conjecture that SARS-CoV-2 may directly infect the keratinocytes in the injured skin (Fig 2).

In summary we noted in 52 patients with COVID-19, that skin manifestation can be present before the onset of fever or can coexist with fever and that angiotensin-converting enzyme 2 and transmembrane serine proteases were coexpressed in stratum granulosum keratinocytes. These findings highlight the potential risk of SARS-CoV-2 transmission via wounded skin in those with skin manifestations of the disease. Hence, recognition of skin lesions associated with COVID-19 by dermatologists and other health care professionals is essential.