LETTER TO THE EDITOR

Transient aquagenic syringeal acrokeratoderma during COVID-19 outbreak: a retrospective case series of eight patients

Editor

Since the outbreak of COVID-19 in December 2019, diverse skin manifestations have been reported to be associated with the disease, most of them concerning skin rashes.[1] We have since identified an increase in the diagnosis of aquagenic syringeal acrokeratoderma (ASA), in consonance with other reports of ASA following excessive exposure to water and disinfectants.[2,3] However, an association between SARS-CoV-2 and ASA has not previously been reported. The objective of this study was to describe cases of ASA presenting during the COVID-19 outbreak and its possible association with SARS-CoV-2 infection.

We retrospectively reviewed patients with a diagnosis of ASA consulting either to the emergency department or to the dermatology outpatient clinic in two third-level referral hospitals from March 2020 to March 2021, including virtual consultations. Diagnosis was established by a board-certified dermatologist through symptoms and a water immersion test, where patients were exposed to warm water for 2 min. Patients with a history of ASA or symptoms beginning previous to March 2020 were excluded. The clinical pattern of ASA was documented regarding both palmar and plantar involvement as well as the presence or absence of symptoms (Fig. 1). Known associated risk factors such as hyperhidrosis, cystic fibrosis or atopic dermatitis were recorded. All patients were asked about COVID-19 symptoms such as fever, cough or dyspnoea. When available, RT-PCR nasopharyngeal swabs for SARS-CoV-2 results were registered. No skin biopsies were performed due to virtual consultation and lack of patients' consent.

The study population comprised 8 patients (3 men and 5 women), with ages ranging from 5 to 34. Demographic and clinical data of the patients are depicted in Table 1. All patients presented with bilateral palmar ASA, while none reported the involvement of the soles. Out of 8 patients, 5 tested positive for SARS-CoV-2 while one reported symptoms compatible with COVID-19 pneumonia, with no PCR available. The former reported onset of ASA days after the diagnosis of COVID-19 infection, while the latter described the beginning of ASA immediately after the first pneumonia symptoms. All of these patients (5) reported no further symptoms of ASA during follow-up after COVID-19 resolution.

Figure 1 Clinical presentation of aquagenic syringeal acrokeratoderma in a patient with SARS-CoV-2 infection. Bilateral palmar involvement with a cobblestone appearance after a 2-min submersion in warm water.

ASA is an uncommon disorder characterized by transient whitish papules and plaques giving a cobblestone appearance to the palms, triggered by exposure to water.[4] The pathogenesis regarding ASA remains unclear. However, histopathological findings reveal dilated eccrine ducts and sweat gland hyperplasia amongst other changes, suggesting a possible dysfunction of sweat glands and the stratum corneum.[5] This hypothesis goes together with ASA's known frequent comorbidities, such as cystic fibrosis, hyperhidrosis and non-steroidal anti-inflammatory drugs; all of which result in increased sweat salt concentrations.

Up till now, reports of ASA during the COVID-19 pandemic have all been associated with an increase in the frequency of daily handwashing.[2,3] However, although increased handwashing may be a probable trigger for ASA, this factor by itself does not explain the fading of ASA symptoms after COVID-19 resolution. Several histopathological studies of COVID-19 patients have reported the presence of an abnormal perieccrine lymphocytic infiltrate in chilblain-like lesions.[6] Furthermore, immunohistochemistry for SARS-CoV-2 spike protein was found to be positive in eccrine sweat glands.[7]

Additionally, a decrease in angiotensin-converting enzyme 2 (ACE-2) function has been reported as a possible cause of COVID-19's prothrombotic effects. Similar to this, ACE inhibitors have been postulated as an associated risk factor of ASA.[4] On this line,

Table 1 Demographic and clinical data of the patients

Patient N°	Sex	Age	Palmar involvement	Symptoms	Associated comorbidities	COVID test	Temporal association with COVID test	Evolution
1	Female	5	Bilateral	No	None	Unknown†	‡	Resolved <2 months
2	Female	5	Bilateral	No	None	PCR +	Onset days after PCR+	Resolved <2 months
3	Male	8	Bilateral	No	None	PCR +	Onset days after PCR+	Resolved <2 months
4	Female	26	Bilateral	Burning	Hyperhidrosis	PCR +	Onset days after PCR+	Resolved <2 months
5	Female	30	Bilateral	Burning	None	Unknown	–	Partial resolution
6	Male	28	Bilateral	No	None	Unknown	–	Resolved <2 months
7	Male	32	Bilateral	No	None	PCR +	Onset days after PCR+	Resolved <2 months
8	Female	34	Bilateral	Pruritus	None	PCR +	Onset days after PCR+	Resolved <2 months

†Reported symptoms compatible with COVID-19 pneumonia after close contact with a positive patient. However, no PCR was performed due to quarantine.
‡Onset during quarantine, days after first pneumonia symptoms.

changes in ACE 2 function during COVID-19 could mimic ACE2 inhibitors action on the sweat glands, triggering ASA symptoms.

The main limitations of our study are its retrospective nature and the small sample size, which contrasts to the number of cases of SARS-CoV-2 infection worldwide, making this association debatable. However, being ASA a mainly asymptomatic condition, it is probable that many patients did not consult. In addition, the lack of universal access to medical virtual consultation and its transitory condition, both may have caused an underdiagnosis of the disease.

Furthermore, none of our cases were confirmed by histopathological analysis due to virtual consultation and lack of patients' consent for a biopsy. However, ASA can easily be diagnosed through clinical symptoms and a water immersion test, such as performed.

These findings suggest a possible association between SARS-CoV-2 and sweat gland dysfunction, which could in turn result in transient ASA symptoms during the course of the disease.

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Data available on request from the authors.

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References
1 Galván Casas C, Català A, Carretero Hernández G *et al*. Classification of the cutaneous manifestations of COVID-19: a rapid prospective nationwide consensus study in Spain with 375 cases. *Br J Dermatol* 2020; **183**: 71–77.
2 Tai Y, Fukumoto T, Oka M, Nishigori C. Frequent handwashing and disinfection: a potential new trigger for aquagenic wrinkling of the palms caused by COVID-19 outbreak. *J Eur Acad Dermatol Venereol* 2021; **35**: e9–e10.
3 Alay H, Bilen H. Aquagenic syringeal acrokeratoderma in an adolescent female with COVID-19. *Rev Soc Bras Med Trop* 2021; **54**: e0152.
4 Luo DQ, Li Y, Huang YB, Wu LC, He DY. Aquagenic syringeal acrokeratoderma in an adult man: case report and review of the literature. *Clin Exp Dermatol* 2009; **34**: e907–e909.
5 Luo DQ, Zhao YK, Zhang WJ, Wu LC. Aquagenic acrokeratoderma. *Int J Dermatol* 2010; **49**: 526–531.
6 Sohier P, Matar S, Meritet JF, Laurent-Roussel S, Dupin N, Aractingi S. Histopathologic features of Chilblainlike lesions developing in the setting of the coronavirus disease 2019 (COVID-19) pandemic. *Arch Pathol Lab Med* 2021; **145**: 137–144.
7 Torrelo A, Andina D, Santonja C *et al*. Erythema multiforme-like lesions in children and COVID-19. *Pediatr Dermatol* 2020; **37**: 442–446.

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