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ORIGINAL ARTICLE

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Presentation and Management of Cutaneous Manifestations of COVID-19

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ABSTRACT

Introduction: The spread of the new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has instigated a fervent race of the medical community to identify its manifestations, the patients at risk, and optimal disease management. While the COVID-19 illness is largely associated with respiratory consequences, there is increased reporting of other organ-specific disease sequelae that include the skin.

Objective: To identify, describe, and classify the main skin manifestations of COVID-19 and associated protocols for management.

Methods: Forty-five patients from three clinical centers in North and South America with positive COVID-19 PCR and/or serology presenting cutaneous manifestations were included in this retrospective chart review. Medical history, biopsies, dermoscopy, laboratory findings, clinical photography, and disease management were documented.

Results: Seven main types of cutaneous manifestations were identified: exanthema/molbilliform, urticaria, papular/pustular/vesicular, petechiae/purpura, livedo reticularis, chilblains, and alopecia. Histopathogical analysis from skin biopsies and/or dermoscopy highlighted an inflammatory or vascular pathophysiology depending on the type of manifestation. While the first three types of COVID-19 skin manifestations preceded or coincided with other symptoms such as anosmia, fever, chills, chilblains, and livedo were found in later disease stages. All cases had a positive resolution with appropriate treatment.

Conclusions: Cutaneous symptoms are part of the COVID-19 disease spectrum. Early identification, diagnosis, and management through a multidisciplinary approach can facilitate safe disease resolution for patients.

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INTRODUCTION

The novel coronavirus disease (COVID-19) emerged in late 2019 in China, spread globally, and was declared a pandemic by the World Health Organization (WHO) in March 2020. It is a zoonotic illness originating in bats and caused by a single-stranded RNA virus known as 2 severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 is primarily transmitted between people through respiratory droplets and contact routes, which is why social distancing and personal protective equipment is recommended to decrease the infectivity.[1] The mean incubation period is 5.2 days and 95% of patients develop symptoms up to 12.5 days after exposure.[2,3]

Patients infected with COVID-19 can present fever, fatigue, dry cough, breathing difficulties, myalgias, sore throat, anosmia, neurologic and gastrointestinal disturbances, such as diarrhea, or be completely asymptomatic.[4-7] The most severe cases develop dyspnea, with or without hypoxemia, a week after the onset of symptoms and deteriorate to acute respiratory distress syndrome (ARDS), disseminated intravascular coagulation, septic shock, and metabolic acidosis. Patients most susceptible to negative outcomes are the elderly and those with comorbidities such as hypertension, obesity, diabetes, and renal failure.[8] There have been some reports that increased COVID-19 viral load, viral dissemination, and severity of lung involvement is androgen-dependent rendering males more vulnerable to the disease but this has yet to be proven.[9,10]

Laboratory findings of COVID-19 infection include leukopenia, thrombocytopenia, elevated interleukin-6 (IL-6) levels, and increased D-dimer levels that increase the risk of venous thromboembolism.[11] Aberrant release of proinflammatory cytokines resulting in cytokine storm syndrome is suggested

to be the underlying pathophysiology in the development of severe disease.[12]

Diagnosis of COVID-19 relies on physical examination, oximetry screening, chest X-rays, and CT scans but laboratory tests provide the definitive diagnosis. RT–PCR-based viral RNA detection is sensitive and can rapidly and effectively confirm early SARS-CoV2 infection.[13] Virus-specific antibody testing can also be helpful for the diagnosis of suspected patients with negative RT–PCR results. Chest X-rays or CT scans can also aid diagnosis: pulmonary radiologic indicators of COVID-19 are changes in the outer zone of the lungs, multiple ground-glass opacity, pulmonary consolidation, and seldomly pleural effusion.[14]

Cutaneous manifestations of COVID-19 such as urticaria, erythematous, petechial rashes and varicella-like cysts have been already reported in a plethora of recent publications.[15-19] In one study up to 20% of COVID-19 patients hospitalized in intensive care were shown to have skin symptoms, though their association with the virus was not verified;[19] thus far, the estimated prevalence of such symptoms ranges from 0.2%–20.4%.[4,20-23] We here report the seven main types of cutaneous manifestations from forty-five patients in three clinical sites in North and South America. The classification can aid dermatologists and other medical specialties to accurately recognize cutaneous symptoms of COVID-19 in a timely manner when screening patients in person or through telemedicine on these manifestations.[7,24]

METHODS

Between 26 March and 16 June 2020, we investigated the epidemiologic and clinical features of cutaneous manifestations in forty-five patients that tested positive for COVID-19. The data were collected prospectively by experienced dermatologists from two dermatologic clinical in Sao Paolo, Brazil (Almeida Dermatology and Arruda Dermatology) and one from New York City, NY, USA (Sadick Dermatology). Patient demographics, dermatologic symptoms, COVID-19 history and symptoms, and past medical history was obtained from all patients. Skin biopsies, CT scans, and blood tests were conducted in patients as deemed appropriate. Since the intent of the prospective study was to obtain information for educational purposes and healthcare delivery, no Institutional Board Review approval (IRB) was required as it was determined to not meet the definition of Human Subjects Research. Written informed consent was obtained from all patients or their caregivers.

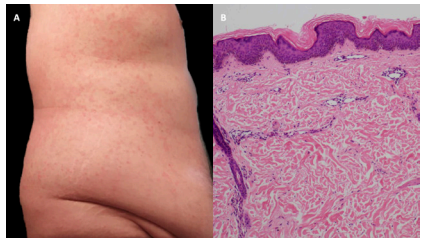
RESULTS

Forty-five patients with cutaneous manifestations who had not started treatment with any new drug in the 15 days preceding lesion onset were referred to the clinic. The average patient age was 37.2±19 (range, 1–68), 55.6% were male, and the majority had comorbidities (atopic dermatitis n=34; cardiac/circulatory conditions n=5, diabetes n=5, asthma n=3, and alopecia n=11). All patients had COVID-19 infection confirmed by RT-PCR and antibody-test. Aside from cutaneous lesions, the most common symptoms amongst patients were fever, anosmia, headache, and diarrhea; 44% (n=20) had no symptoms. Average time until resolution of symptoms was 9.2 days (Supplemental Table 1).

Seven types of cutaneous manifestations were observed: exanthematous/molbilliform, urticaria, maculopapular/pustular, petechiae, livedo reticularis, chilblains, and telogen effluvium. These were not mutually exclusive, as more than one type could present within the same patient.

Exanthematous/molbilliform: Five patients (11%) presented exanthematous/molbilliform rash, characterized by monomorphic papulo-vesicular lesions (Figure 1A). These most commonly were found on the trunk, face, hands, and feet. Pruritis was present in three patients and the symptoms appeared 2–3 days prior to the appearance of other systemic symptoms such as fever. Histological analysis showed dilation of the superficial dermal plexus and a mild lymphocytic perivascular infiltrate without vasculitis (Figure 1B).

FIGURE 1. (A) Exanthema in 34-year old male patient (patient number 1). (B) Histology of exanthematous rash revealing dilated blood vessels surrounded by discrete perivascular lymphocytic infiltrate and neutrophils (heamatoxylin-eosin/Bars=100 mm).



Urticaria/Erythema: Nine patients (20%) presented urticaria. Generalized and partially confluent wheals surrounded by mild erythema were present in the face, trunk, and extremities (Figure 2A). Moderate to severe pruritus often coexisted. Urticaria was either the only symptom or preceded the onset of systemic symptoms by 24–48 hours. Histological analysis revealed an interface dermatitis with lymphocytic vasculitis of the superficial plexus, characterized by foci of red cells extravasation (Figure 2B).

FIGURE 2. (A) Urticaria in 38-year-old female patient (patient number 24; Table 1). (B) Biopsy showed extremely dilated vessels were observed in the dermis with intense perivascular lymphocytic and neutrophils infiltrate with a partial compromise of the vascular wall (heamatoxylin-eosin/Bars=100 mm).

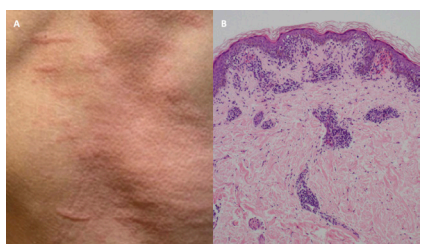


FIGURE 3. (A) Papular/pustular rash in 41-year-old male patient (patient number 39; Table 1). (B) The biopsy of affected skin showed superficial and deep perivascular dermatitis with cuffs of lymphocytes surrounding blood vessels in a vasculitic pattern along with occasional infiltrating eosinophils and neutophils (heamatoxylin-eosin/Bars=40 mm).

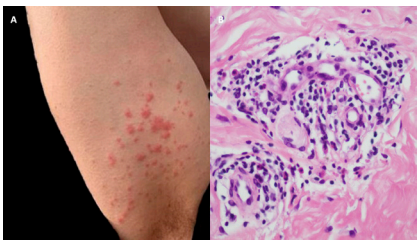
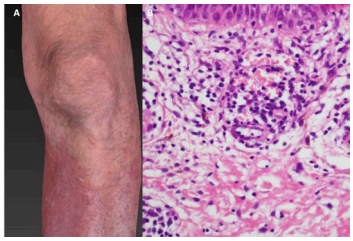


FIGURE 4. (A) Petechia in 68-year-old male (patient 36; Table 1) (B) The biopsy of affected skin showed interstitial edema in the papillary dermis and superficial vascular plexus. Blood vessels were dilated with perivascular lymphocytic infiltrate affecting the vessel wall associated with erythrocytes, leukocytes and eosinophils, therefore featuring a small vessel lymphocytic vasculitis (heamatoxylin-eosin/Bars=100 mm).



Papular/Pustular: Twenty-three patients (51%) presented papular or pustular eruptions. This widespread papular/pustular eruption characterized by vesicobullous or pustular lesions and indurated pigmented nodules, appeared concomitantly or a few days after the onset of other symptoms (Figure 3A). Histopathology of pustular lesions showed lymphocytic infiltrate around dilated blood vessels with eosinophils, without damage of the vessel wall (Figure 3B).

Petechiae/Vasculitis: Six patients (13%) presented petechiae. These petechial rashes had purpuric lesions up to 2 mm, or areas of vasculitis with or without fever (Figure 4A). In our group of patients, this manifestation was associated with more severe cases of the disease that also presented laboratory abnormalities (high D-dimer, C-reactive protein). Histopathology of this type of lesion was characterized by dense lymphocytic infiltrate with vascular damage of the superficial plexus (Figure 4B).

Livedo Reticularis: Two (4%) patients showed livedo reticularis (Figure 5A). Both cases presented later in the disease course and were accompanied by abnormal laboratory values including elevated levels of D-dimer, and clinical symptoms such as fever and difficulty breathing. Histological analysis from biopsies showed ectasia of blood vessels of small and medium caliber, with little or no inflammation (Figure 5B).

FIGURE 5. (A) Alopecia in 31-year-old male patient (patient 19; Table 1). (B) The biopsy of affected skin showed dilation and congestion of superficial vascular plexus without compromising the vessel wall with perivascular lymphocytic infiltrate and reduced in number of hair follicles with discrete proliferation of fibroblasts and thin collagen fibers forming parallel bundles in the isthmus of some follicles (heamatoxylin-eosin/Bars=100 mm). (C) Dermoscopy of affected area showed decreased hair density with presence of empty follicles.

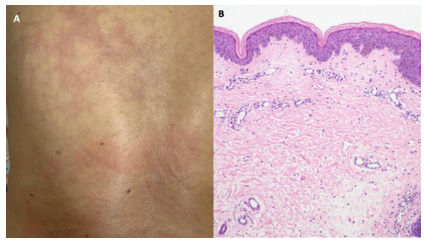


FIGURE 6. (A) Livedo reticularis in 52-year-old female patient (patient 30; Table 1). (B) Histopathological examination showed dilated blood vessels, with little or none inflammation. (heamatoxylin-eosin/Bars=100 mm).

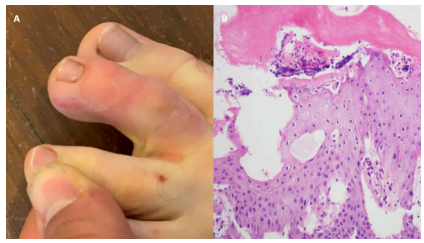
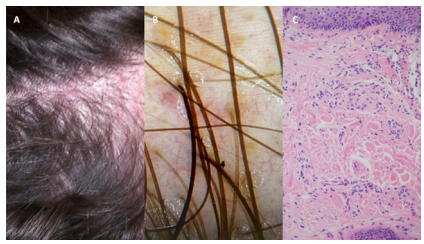


FIGURE 7. (A) Chilblain in 25-year-old male patient (patient 13; Table 1). (B) The biopsy of affected skin showed vesicular spongiotic dermatitis with keratinocyte necrosis associated with a superficial perivascular lymphocytic infiltrate in the toe injury fragment (heamatoxylin-eosin/Bars=100 mm).



Chilblains: Seven patients (15.6%) had chilblains predominantly appearing in the toes (Figure 6A). Chilblains were the only clinical symptom in the majority of the patients. Histopathology of the affected area showed vesicular spongiotic dermatitis with keratinocyte necrosis, of a dyshidrotic pattern, associated with a superficial perivascular lymphocytic infiltrate (Figure 6B).

Telogen Effluvium: Ten patients (22.2%) presented telogen effluvium (Figure 7A) a few days following the onset of systemic symptoms. This was diagnosed with pull test, trichoscopy, and scalp biopsy (Figure 7B). Histological analysis showed edema and dilation of the superficial vascular plexus and absence of inflammation (Figure 7C).

Treatment of cutaneous lesions was done in the context of a multidisciplinary approach with other specialties, taking into account patient comorbidities and the presence of other systemic symptoms. The general treatment algorithm included a course of antihistamines and topical steroids for cases with pruritus and erythema. Macrolide-type antibiotics such as azithromycin were introduced in cases with laboratory alterations, and/or one or more clinical symptom according to the general practice recommendations for COVID-19 management.[25-29] In the presence of signs vasculitis in clinical and/or dermatoscopic signs of purpura, petechia, and subsequent ulceration, laboratory tests including a partial thromboplastin time (PTT), activated partial thromboplastin time (aPTT), lactate dehydrogenase, ferritin, C-reactive protein, antiphospholipid, lupus anticoagulant, and D-dimer were conducted. In cases with elevated markers such as D-dimer, oral steroids were introduced with caution to mininmize the risk of aggravating pruritus, severe exanthematous rash/urticaria, and angioedema. Moreover, the introduction of oral steroids should be weighed against other systemic symptoms as it has been noted that steroid-dependent immunosuppression increases viral shedding.[30]

DISCUSSION

SARS CoV-2 mainly causes respiratory symptoms, but like any other virus can have a series of cutaneous manifestations. Since the emergence of reports regarding COVID-19-related cutaneous manifestations, dermatologists have been hypervigilant in identifying skin lesions suggestive of COVID-19 infection and prompting patients to get tested by RT-PCR and/or antibody testing. As such, in this report, we studied forty-five patients positive for COVID-19 who were referred to our clinics and followed them from COVID-19 diagnosis to treatment/disease resolution. We identified seven main types of COVID-19-associated cutaneous manifestations that appeared in different times in the course of the disease and were associated with different disease severity. Our findings corroborate with reports from other authors regarding the main types of COVID-19-related lesions.[22,31-33]

Exanthematous rashes, urticaria, and papular/pustular eruptions presented early in the disease or before the onset of any other clinical sign. The duration of these symptoms was relatively short-lived and managed well with a combination of topical steroids/antihistamine and azithromycin.

Livedo reticularis, petechiae, chilblains, and telogen effluvium were also observed. Most often than not, these latter symptoms appeared after the onset of fever, fatigue, and other COVID-19-related systemic symptoms and were associated with abnormal laboratory values (lymphopenia) in mild/moderate cases. None of our cases had a severe hypercoagulable state leading to disseminated intravascular coagulation (DIC) with acral ischemia and dry gangrene. The livedoid type lesions were indicators of more severe disease whereas the chilblains were observed in mild cases. Telogen effluvium presented suddenly in patients that had other cutaneous symptoms. Four of the ten patients with telogen effluvium had pre-existing hair disorders (alopecia areata, androgenetic alopecia).

The pathophysiology of the COVID-19 cutaneous manifestations has not been elucidated. While urticaria/exanthema/papular-pustular lesions are hypothesized to have an inflammatory etiology, it is unclear where this is a secondary consequence of SARS- CoV-2 infection, a post viral immunological reaction or a primary infection of the skin due to the presence of viral nucleotides. There have been reports of COVID-2 binding ACE2 receptors in the skin vessels, as well as in the basal layer of the skin but we did not detect any viral particles during our histopathological analysis.[34] Livedoid/petechiae and chilblain-type lesions are thought to have a vascular pathogenesis due to direct viral replication in the vascular endothelium or occur secondary to the induction of autoimmunity, a concomitant cytokine storm and release of C5b-9, C4d, and MASP2, leading to microvasculature thrombosis in the skin.[35] Telogen effluvium is known to occur in response to viral infections,[36,37] and while the exact etiology is unclear, we hypothesize that in our cases the cause was hypoxia and localized follicular vasoconstriction.

In the past few months, a remarkable amount of progress has been achieved by the dermatological community with the collective goal of identifying dermatological symptoms related to COVID-19 and their management, particularly in patients with inflammatory dermatoses or those on immunosuppressants.[38,39] As of now, whether individuals of specific genetic background, are more or less at risk is not known, and only through large number of cases and retrospective epidemiological studies will we be able to disseminate the ''who'' and ''why'' and ''how'' someone manifests cutaneous or other COVID-19 symptoms. Of note, we did not see in our cases male predominance presenting cutaneous manifestations, or any particular dermatologic comorbidity specifically correlated with a particular type of cutaneous eruption.

CONCLUSION

In conclusion, our report adds to the body of evidence that COVID-19 cutaneous presentations can be highly variable and can precede other symptoms and/or manifest in mild/asymptomatic cases. Thus, they could be the only clue to the diagnosis and thereby crucial to be recognized promptly by dermatologists to avoid community propagation of COVID-19. Rashes and lesions could be the seasonal flu, an allergic reaction, herpes-zoster or simplex, dengue, drug hypersensitivity, or COVID-19; heightened awareness of the most common forms of COVID-19 cutaneous lesions, and their prognosis/management is something that not only dermatologists, but the medical community needs in order to ensure the optimal clinical outcomes for our patients.

DISCLOSURES

The authors declare no conflict of interest. The authors received no funding for this work.

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SUPPLEMENTAL TABLE 1.

Patients Baseline Demographics and Disease Characteristics (n: 40)

Pt N	Age	Gender	Comorbidities	Symptoms	Cutaneous Pattern	Complementary Exam	Treatment	Outcomes
1	34	M	AD Asthma Obesity SAH	None	Exanthematous rash/morbiliform: chest, abdomen, arms, hands, fingers 25-50% total body	SatO2 100-94%	Oral antihistamine Oral azithromycin	Resolution after 8 days
2	48	M	AD	Anosmia on the 3th day and diarrhea on 5th day	Exanthematous rash/morbiliform: chest, abdomen, arms with pruritus 25-50% total body	SatO2 100-94%	Oral antihistamine Oral azithromycin	Resolution after 5 days
3	12	F	AD	Fever for 2 days, diarrhea for 5 days and pruritus	Exanthematous rash/morbiliform: chest, abdomen, flexural areas 25-50% total body	SatO2 100-94%	Oral antihistamine Oral azithromycin	Resolution after 6 days
4	43	M	AD	Sore throat and anosmia for 4 days Fever 2th day Pruritus	Exanthematous rash: lower legs <25% total body	Low fibrinogen High troponin High CPK Chest CT: ground glass opacities SatO2 100-94%	Oral antihistamine Oral azithromycin	Resolution after 10 days
5	31	M	Vitiligo AGA	None	Erythematous rash papular/ pustular/vesicular: genital first and hands 5 days later <25% total body	SatO2 100-94%	Oral azithromycin	Resolution after 10 days
6	34	M	AD AGA	None	Erythematous rash papular/ pustular/vesicular: axillary area, arms, chest associated with follicular pattern on the hair and intense pruritus <25% total body	SatO2 100-94%	Oral antihistamine Oral azithromycin	Resolution after 8 days
7	46	F	AD	None	Erythematous rash papular/ pustular/vesicular: face with pruritus <25% total body	SatO2 100-94%	Oral antihistamine Oral azithromycin	Resolution after 15 days
8	43	F	AD	None	Erythematous rash papular/ pustular/vesicular: face, abdomen, back and arms <25% total body	SatO2 100-94%	Oral antihistamine Oral azithromycin Oral corticosteroid	Resolution after 6 days
9	3	M	AD	None	Erythematous rash papular/ pustular/vesicular: buttocks with 3 days of pruritus <25% total body	SatO2 100-94%	Oral antihistamine Oral azithromycin	Resolution after 10 days
10	16	F	AD	Fever for 2 days	Erythematous rash papular/ pustular/vesicular: arms <25% total body	Chest CT: ground glass opacities SatO2 100-94%	Oral antihistamine Oral azithromycin	Resolution after 10 days
11	65	M	AD	Diarrhea for 2 days	Erythematous rash papular/ pustular/vesicular: arms, hands, fingers and feet <25% total body	SatO2 100-94%	Oral antihistamine Oral azithromycin Oral corticosteroid	Resolution after 10 days
12	59	M	AGA	Fever and dry cough for 7 days	Erythematous rash papular/ pustular/vesicular rash thorax and scalp <25% total body	Leukocytosis Neutrophilia Thrombocytopenia High PT High D-dimer Low fibrinogen High CRP Chest CT: ground glass opacities SatO2 100-94%	Oral antihistamine Oral azithromycin	Resolution after 7 days after our protocol and 18 days total
13	25	M	AGA	None	Erythematous rash papular/ pustular/vesicular and vascular rash Pseudo chilblain: ear, feet and toes Follicular rash in hair 25-50% total body	Neutropenia High PT Low fibrinogen Normal D-dimer Normal chest CT SatO2 100-94%	Oral antihistamine Oral azithromycin Topic corticosteroid	Resolution after 7 days
14	25	M	AD AGA	Fever for 1 day, diarrhea, fatigue and dry cough for 5 days	Erythematous rash papular/ pustular/vesicular rash hair, beard and trunk <25% total body	SatO2 100-94%	Oral antihistamine Oral azithromycin Topic corticosteroid and ketoconazole shampoo	Resolution after 12 days
15	25	F	AD AGA	Fever, diarrhea and headache for 2 days, fadigue and dry cough for 3 days	Erythematous rash papular/ pustular/vesicular rash: hair <25% total body	SatO2 100-94%	Oral antihistamine Oral azithromycin	Resolution after 7 days
16	18	M	AD	Fever for 2 days	Erythematous rash Telogen effluvium: hair <25% total body	SatO2 100-94%	Oral antihistamine Oral azithromycin	Resolution after 5 days
17	16	F	AD	Fever for 1day	Erythematous rash Telogen effluvium: hair <25% total body	SatO2 100-94%	Oral antihistamine Oral azithromycin	Resolution after 7 days
18	40	M	AD AGA	None	Erythematous rash Telogen effl uvium: hair, beard <25% total body	High D-dimer SatO2 100-94%	Oral antihistamine Oral azithromycin	Resolution after 10 days

SUPPLEMENTAL TABLE 1. (CONTINUED)

Patients Baseline Demographics and Disease Characteristics (n: 40)

Pt N	Age	Gender	Comorbidities	Symptoms	Cutaneous Pattern	Complementary Exam	Treatment	Outcomes
19	31	M	AD AA	None	Erythematous rash Telogen effluvium: hair, beard and perioral <25% total body	Neutrophilia High PT SatO2 100-94%	Oral antihistamine Oral azithromycin	Resolution after 8 days
20	30	F	AD AGA	None	Telogen effluvium: hair Papular/ pustular/ vesicular: neck <25% total body	Thrombocytopenia Low fibrinogen SatO2 100-94%	Oral antihistamine	Resolution after 5 days
21	31	M	AD AGA	None	Telogen effluvium: hair Erythematous papular/pustular/vesicular: face and neck <25% total body	SatO2 100-94%	Oral antihistamine	Resolution after 7 days
22	18	M	AD	None	Urticarial rash blanching and angioedema Papular/pustular/vesicular Follicular erythematous rash Telogen effluvium: hair <25% total body	High D-dimer SatO2 100-94%	Oral antihistamine	Resolution after 12 days
23	31	M	AD AGA	Fever, headache and dry cough for 5 days	Urticarial rash blanching: face, chest, abdomen, back, arms on the first episode Urticarial vascular non blanching: legs; Papular/pustular/vesicular: fingers and toes; Erythematous rash Telogen effluvium: hair; on the second episode >50% total body	High ESP High CRP Neutrophilia SatO2 100-94%	Oral antihistamine	Resolution after 7 days, recurrence after 1 month with no other symptoms and recovered after 5 days
24	38	F	AD	Fever for 1 day, diarrhea for 2 days	Urticarial rash blanching: arms, hands, abdomen, back and legs >50% total body	High CRP SatO2 100-94%	Oral antihistamine	Resolution after 10 days
25	54	F	AD	Fever for 2 days, sore throat for 3 days and anosmia for 7 days	Urticarial rash blanching: face, neck, arms, hands, abdomen, legs and feet 25-50% total body	Leukocitosis SatO2 100-94%	Oral antihistamine	Resolution after 10 days
26	37	F	AD	27 weeks pregnant evolution with pneumonia	Urticarial rash blanching: neck arms and legs <25% total body	High D-dimer High ferritin High fibrinogen High CRP Chest CT: ground glass opacities SatO2 100-94%	Oral antihistamine Oral azithromycin	Resolution after 10 days
27	5	F	AD	None	Urticarial vascular rash non blanching with angioedema: face, chest, abdomen, back, genital, buttocks, arms, hands, fingers, legs, foot and toes >50% total body	Leukocitosis SatO2 100-94%	Oral antihistamine Oral azithromycin	Complicated with angioedema and after treatment, resolution after 9 days
28	20	M	AD Cardiomyopathy	None	Urticarial vascular rash non blanching: abdomen left side, legs and feet unilateral <25% total body	Low potassium Low calcium Low magnesium SatO2 100-94%	Oral antihistamine Oral azithromycin	Resolution after 7 days
29	36	F	AD	None	Urticarial vascular rash non blanching: arms, chest, abdomen, back, buttocks, legs and feet >50% total body	SatO2 100-94%	Oral antihistamine Oral azithromycin	Resolution after 5 days
30	52	F	Asthma	Dyspnoea	Erythematous rash papular/ pustular/vesicular: chest, hands and fingers Livedo reticularis rash: back <25% total body	High D-dimer Chest CT: normal SatO2 100-94%	Oral antihistamine Oral azithromycin Oral corticosteroid Topic corticosteroid	Resolution after 8 days
31	66	F	AD	Fever and dyspnoea for 2 days in the beginning. After 8 days, diarrhea for 5 days complicated with acute diverticulitis	Livedo reticularis rash: legs <25% total body	Leukocitosis High gamaGT High PT High CRP High D-dimer Dengue serology negative Chest CT: ground glass opacities SatO2 100-94%	None	Resolution after 8 days
32	10	M	AD	None	Vascular rash Pseudo chilblain: toes with pruritus <25% total body	SatO2 100-94%	Oral antihistamine Oral azithromycin	Resolution after 7 days
33	17	F	AD	None	Vascular rash Pseudo chilblain: toes <25% total body	High PT High CRP Neutrophilia Thrombocytopenia SatO2 100-94%	Oral antihistamine Oral azithromycin	Resolution after 15 days
34	1	F	AD	None	Vascular rash Pseudo chilblain: fingers <25% total body	SatO2 100-94%	Oral azithromycin	Resolution after 5 days
35	62	M	SAH Obesity	None	Vascular rash Pseudo chilblain: toes <25% total body	SatO2 100-94%	Oral azithromycin	Resolution after 11 days

SUPPLEMENTAL TABLE 1. (CONTINUED)

Patients Baseline Demographics and Disease Characteristics (n: 40)

Pt N	Age	Gender	Comorbidities	Symptoms	Cutaneous Pattern	Complementary Exam	Treatment	Outcomes
36	68	M	SAH	Diarrhea for 2 days and persistent intense pruritus	Vascular rash Petechiae: back, legs, 25-50% total body	Leukocitosis Lymphopenia Neutrophilia Syphilis negative SatO2 100-94%	Oral azithromycin	Resolution after 12 days
37	91	F	SAH Obesity DM Alzheimer	None	Vascular rash Petechiae: face, ear, sacral and leg <25% total body	High D-dimer SatO2 100-94%	Oral antihistamine Oral azithromycin	Resolution after 9 days
38	49	M	AD Vascular benign brain tumor	Fever for 2 days, diarrhea and headache for 5 days	Erythematous rash papular/ pustular/vesicular: elbow with pruritus Vascular rash Petechiae/pseudo chilblain: arms, hands, legs, feet, toes Telogen effluvium: hair 25-50% total body	Neutrophilia High ESR Low IL-6 High AST High ALT Normal Chest CT SatO2 100-94%	Oral antihistamine Oral azithromycin	Resolution after 12 days New episode of Erythematous rash Papular/Pustular/vesicular after the recover with residual neuropathy peripheral on the leg
39	41	M	AD	Diarrhea for 2 days	Erythematous rash papular/ pustular/vesicular and Vascular rash Petechiae: flexural areas, elbow, hands, fingers, feet 25-50% total body	High CRP SatO2 100-94%	Oral antihistamine Oral azithromycin	Resolution after 10 days
40	49	F	AD	Anosmia on the 1th day	Erythematous rash papular/ pustular/vesicular: arms and hands Vascular rash Petechiae: face, neck, chest, abdomen, back, arms, hands, fingers, legs, feet, toes Telogen effluvium: hair >50% total body	High CRP High ESR Negative serology Syphilis, Dengue virus, Varicella Zoster virus, Herpes simplex virus SatO2 100-94%	Oral antihistamine Oral azithromycin	Resolution after 18 days
41	34	F	None	Headache and fatigue	Urticaria on 50% of the body (extremities and trunk)	SatO2 100-94%	Oral antihistamine for 14 days	Resolution after 10 days
42	28	M	AD	One day of diarrhea, fadigue and dry cough for 3 days	Papular/ pustular/vesicular: face, arms and legs <25% total body	SatO2 100-94%	Oral antihistamine Oral azithromycin Topic corticosteroid and ketoconazole shampoo	Resolution after 12 days
43	70	M	Obesity	Fever, headache for 3 days, dry cough for 5 days	Exanthema on the trunk	Leukocitosis High gamaGT High PT High CRP High D-dimer Dengue serology negative Chest CT: ground glass opacities SatO2 100-94%	Oral azithromycin	Resolution after 10 days
44	66	M	Diabetes	None	Vascular rash Petechiae/pseudo chilblain: toes <25% total body	High PT High CRP Neutrophilia Thrombocytopenia SatO2 100-94%	Oral antihistamine Oral azithromycin	Resolution after 15 days
45	55	F	Hypertension	None	Papular/ pustular/vesicular: arms, hands, feet and trunk <25% total body	SatO2 100-94%	Oral antihistamine Oral azithromycin	Resolution after 10 days

N: number of patients; AD: atopic dermatitis; SAH: systemic arterial hypertension; CPK: creatine phosphokinase; CT: computer tomography; SC: subcutaneous; AGA: androgenetic alopecia; PT: prothrombin time; CRP: c-reactive protein; AA: alopecia areata; ESP: erythrosedimentation pale; Gama GT: gama glutamic transferase; DM: diabetes mellitus. Drug doses: oral antihistamine (desloratadine) 5mg for 14-60 days, azithromycin (500 mg/5 days), oral corticosteroid (prednisone) 20/20/10/10 mg`