INTRODUCTION

For almost one year now, the world has been plagued by a novel coronavirus, SARS-CoV-2, causing a new viral infection identified as COVID-19. This virus initially started in Wuhan, China, in December 2019, before rapidly spreading to the rest of the world, triggering a pandemic of extensive morbidity and mortality. 1,2

During this pandemic, an increase in PPE use and hygiene measures (hand sanitizer gels, hand washing) have been mandatory, increasing the frequency of associated dermatological diseases. 3 In addition, there are various exanthems and cutaneous findings that are attributed to the viral infection itself. However, new manifestations of cutaneous eruptions are being reported regularly, although the virus has not yet shown any dermotropism. 3-5

Moreover, dermatological adverse reactions to prescribed or to over-the-counter treatment regimens have been reported as well. 2,3

Therefore, the objective of this study is to identify and compile a list of all those skin disorders which have been reported thus far as a result of this pandemic.

METHODS

A search was made on PubMed and included the terms “COVID-19”, “COVID-2019”, “SARS-CoV-2”, “skin”, “rash”, “cutaneous manifestations”, “Dermatology”, “Derm”, “PPE”, “Chilblains and COVID”, “Erythema Multiforme and COVID”, “Maculopapular Rash and COVID”, “Vesicular Rash and COVID”, “Herpetiform Rash and COVID”, and “Multisystem Inflammatory Syndrome In Children.”
COVID", "Chickenpox-like Rash and COVID", "Urticaria and COVID", "Urticariaform Lesions and COVID", "Petechia and COVID", "Petechial Rash and COVID", "Pityriasis Rosea and COVID", "Multi-System Inflammatory Syndrome", "PPE and COVID", "Hair and COVID", "Pruritus and COVID".

All articles pertaining to skin diseases related to this pandemic were included.

3 | RESULTS

Our search yielded 92 articles, which include those that pertained specifically to the skin findings related to either the viral infection and its treatment or to preventative measures. The remaining articles were not included since they were either related to changes in dermatology clinical practice or to other topics related to dermatology in this pandemic, yet do not discuss skin findings encountered during this pandemic.

3.1 | COVID-19 skin manifestations

Multiple skin findings associated with the viral infection have been reported and are as follows:

3.1.1 | Chilblain or chilblain-like-lesions and acro-ischemic lesions

The most commonly described skin manifestation is chilblain, or chilblain-like acral lesions (CLL). According to one of the studies where 277 patients presented to the outpatient department with skin findings during the first wave of the pandemic, 75% were found to have chilblains. They were described in multiple studies or case reports, as acral, erythematous, or purplish infiltrated papules or plaques. These lesions are usually symptomatic, with pain and/or pruritus being the most common symptoms. The most frequent location was the feet alone, but lesions occurring on both the hands and the feet, the hands alone or the ears were encountered as well. The lesions persisted for a median of 14 days. Treatment was mainly symptomatic with oral antihistamines or analgesics. Most of the patients were young, healthy subjects (children, adolescents, or young adults), with an otherwise asymptomatic or pauci-symptomatic course. Extracutaneous symptoms were occasionally present, but not always. The most common of these were fever, sore throat, and cough. CLL occurred before, concurrently or after the extracutaneous symptoms, when present. No significant gender predilection was observed. Due to testing restrictions, many of the patients in the studies were not tested with nasopharyngeal polymerase chain reaction (PCR) swabs. Many patients with CLL had a workup for underlying autoimmune diseases and coagulopathies, which was negative. Histopathological studies of skin biopsies from these lesions showed a dense superficial and deep perivascular and peri-ecrine lymphocytic infiltrate with no vasculitis in two reports. However, in another case series, histopathological studies revealed lymphocytic vascular damage as a hallmark of CLL. Their findings on 7 skin biopsies ranged from mild vasculitic disease, where there was a faint vascular wall lymphocytic infiltrate, to severe fibrinoid necrosis and thrombosis of the vessels. Furthermore, immunohistochemistry (IHC) studies showed that the lymphocytic inflammatory infiltrate was mainly composed of mature T helper cells.

Another related finding is that of the acro-ischemic lesions described in multiple patients as petechial or purpuric plaques, with the potential to transform into hemorrhagic bullae and necrotic plaques. They affect the lower extremities, including the toes and the soles, more commonly than the upper extremities. They were seen in adults, usually an older population than with chilblains, around one to two weeks following the onset of pneumonia. The lesions were commonly painful or pruritic. On further workup, the patients had elevated D-dimer and a positive SARS-CoV-2 PCR. And on histopathological studies, ischemic necrosis affecting the epidermal and dermal layers and neutrophilic infiltration of blood vessel walls was seen. These lesions resolved spontaneously in two weeks.

3.1.2 | Maculopapular rash

A maculopapular rash is the second most common skin finding associated with the viral infection, and it was reported by multiple sources. The primary lesions in this rash are erythematous, confluent, and blanching macules and papules. The trunk is the most affected site, and however, involvement of the limbs, neckline, and inguinal area was also reported. In one case report, mucosal involvement was also present in the form of aphthous ulcers on the tonsil. Most affected patients were adults with a positive PCR for the SARS-CoV-2 virus and symptoms consistent with pneumonia. The rash was asymptomatic in most, with a few cases reporting pruritis or localized burning pain. Histopathological studies of skin biopsies from a few cases showed mild spongiosis and a mild superficial perivascular lymphocytic infiltrate.

3.1.3 | Herpetiform or vesicular lesions

Another commonly reported skin manifestation is a herpetiform or vesicular eruption similar to what is seen in Herpesviridae infections. It has been described in multiple reports as a vesicular rash, sometimes associated with pustular or papular lesions. The distribution was either generalized or localized, with lesions of different stages in the generalized form, and monomorphic, same-age lesions in the localized form, mostly limited to the chest area. In a few cases, palms and soles were affected. According to the reports, it was
mostly seen in middle-aged and older adults, although one case of an 8-year-old girl was reported. The most common extracutaneous associated symptoms with herpetiform or vesicular eruptions were pneumonia, fever, cough, headache, and weakness. The rash appeared after the COVID-19 diagnosis, confirmed by nasopharyngeal swab PCR testing, with a latency period averaging 2 weeks, but reaching up to a month. In the majority of patients, the vesicular rash was pruritic. In a report of three cases where a skin biopsy was done around 6–10 days after the onset of the rash, the most common features were intraepidermal vesiculation, dyskeratosis, acantholysis, suprabasal clefting, mild dermal inflammatory infiltrates, and dermal eosinophils. Direct Immunofluorescence (DIF) done on one of the specimens was negative.

### 3.1.4 | Urticaria

An additional cutaneous finding associated with infection with the SARS-CoV-2 virus is the urticariform rash. Multiple reports describe patients who presented with pruritic urticariform lesions (Figures 1 and 2), and who were found to be positive by PCR for COVID-19 infection. The most common extracutaneous finding was fever. Other symptoms including malaise, myalgias, cough, rhinorrhea, and dyspnea were also commonly reported. These symptoms occurred concomitantly with the cutaneous eruption or preceding it. Additionally, in some cases, the urticaria was associated with angioedema, affecting the eyelids, lips, and hands. The mainstay of treatment was oral antihistamines, with marked improvement or even resolution of symptoms. One patient also received favipiravir and hydroxychloroquine in addition to antihistamines, as a treatment for his COVID-19. None of the reported patients had a skin biopsy and therefore no histopathological studies were done of these urticariform eruptions.

### 3.1.5 | Petechial and purpuric rash

A few case reports also identified patients with either a petechial or a purpuric rash in PCR-confirmed cases of COVID-19 (Figures 3-5). Interestingly, one of the cases was initially attributed to Dengue fever, but was later found to be related to a COVID-19 infection. Both necrotic and non-necrotic purpura were evident in patients with COVID-19. The purpura was described in a few reports as being retiform and associated with hemorrhagic bullae, or evolving from petechiae into hemorrhagic bullae and necrotic plaques. The petechial rash was most commonly preceded by respiratory symptoms, including pleuritic chest pain and shortness of breath, by around a few days to one week. Patients affected included children and adults. In one case, the affected areas included the flexures and the lower part of the abdomen in addition to the lower extremities. Histopathological studies on skin biopsies from the lesions showed a wide array of different findings, ranging from superficial perivascular lymphocytic infiltrate with red blood cell extravasation and absence of thrombotic vasculopathy, to small vessel vasculitis and vasculopathy. DIF studies showed deposition of IgM, C3, and fibrinogen in dermal blood vessel walls.

### 3.1.6 | Livedo and necrosis

Livedo and necrotic lesions appeared in elderly patients with COVID-19, and in those with more severe disease. These occurred anytime during the course of the disease. In one report, the prevalence of livedo and/or necrotic lesions among COVID-19 patients was 6%. The pathophysiology behind these was most probably the major systemic occlusive vascular disease that occurred in the patients.

### 3.1.7 | Erythema-multiforme-like lesions

Additional skin manifestations related to this viral infection include erythema multiforme (EM)-like lesions that were described as fixed targetoid or annular plaques with a dusky center, affecting the extremities and trunk in most cases, and generally affecting the face and mucous membranes. This was seen in both children and adults, with the mean age in adulthood being around 66 years of age. The rash mostly followed the viral symptoms by an average of two to three weeks. Histological examination of skin biopsies
from these lesions showed mild-to-moderate epidermal spongiosis, erythrocyte extravasation in the dermis, dilated vessels with neutrophil predominance, as well as a perivascular and interstitial lymphocytic infiltrate. In most of these cases, testing for Herpes Simplex Virus by PCR and/or Mycoplasma pneumoniae by serologies was found to be negative.
3.1.8  |  Pityriasis-rosea-like lesions

Another skin manifestation is the pityriasis-rosea (PR) or PR-like eruption. The eruption was described by multiple reports to be pruritic and consisting of oval or round shaped, erythematous and scaly, patches or plaques, with a surrounding collarette of scale.54-58 Most of the patients reported to have PR-like eruption were healthy young adults aged between 23 to 26 years old, with one report of a 39-year-old patient.54-57 The rash was noted a few days after the onset of COVID-19 symptoms, which were most commonly cough and fever, and up to 6 weeks following them.54,55 In a few cases, patients were asymptomatic with a PR-like eruption, who were later found to have a positive SARS-CoV-2 PCR test.57 Laboratory evaluation with a complete blood count and basic metabolic panels were normal in most of the patients, except for one who was found to have lymphopenia.54-57 No histopathological studies on skin biopsies were reported. Patients were treated with either monotherapy or a combination of antihistamines and/or topical steroids, with notable improvement.54,56,57

3.1.9  |  Pruritus

Data about pruritus in this pandemic is still scarce, but it is an important symptom that occurs either alone or with the multitude of dermatoses encountered and significantly affects the quality of life of patients. No studies have assessed the epidemiological characteristics of pruritus related to the pandemic, but according to one report, the underlying causes of itching are multiple and can be classified into three major groups: itch related to the viral-induced or viral-related dermatoses, pruritus secondary to chemical use and PPE wear, and finally, that related to psychosocial stress resulting from the pandemic (Figures 6-10).

3.1.10  |  Multisystem inflammatory syndrome

One important syndrome encountered during this pandemic with temporal association with the virus is the multisystem inflammatory syndrome in children (MIS-C), also known as Kawasaki-disease-like syndrome, described in multiple reports to involve numerous organ systems, and characterized by fever, hemodynamic instability, lymphadenopathy, gastrointestinal symptoms, conjunctivitis, and variable mucocutaneous manifestations, including lip and tongue mucositis, cheilitis, palmoplantar erythema, and several types of cutaneous manifestations such as urticariform, purpuric, targetoid, or morbilliform rashes.60-62 It affects children in the majority of cases, except for one case report in an adult.60-62 Laboratory findings in these patients show elevated inflammatory markers and lymphopenia and other cytopenias.62,64 Many treatments are given to these patients, including antibiotics, immunomodulators, corticosteroids, and supportive care.60-64

3.1.11  |  Isolated cases of cutaneous and nail findings

Refer to Table 1-Isolated Cases of Cutaneous and Nail Findings.

3.1.12  |  Hair findings

Anagen and telogen effluvium

Multiple reports have described anagen and telogen effluvium in patients with PCR-confirmed SARS-CoV-2 infection. These entities affected white, middle-aged adults with a mean age of 48 years old, who were mostly women, and the majority of whom were febrile and many had other dermatologic findings. These patients also received multiple treatments, including paracetamol, corticosteroids, antivirals, antimalarials, antibiotics, and immunomodulators. The onset of hair findings followed that of the viral symptoms by 30 to 60 days, with a mean latency of 57 days.65-67 Hair shedding was severe in most of the cases, as assessed by the Sinclair Shedding Scale, and the disease sometimes remained active one month later.66 Most of these patients were prescribed topical minoxidil, although some received oral nutricosmetics or platelet-rich plasma injections.65,66

Androgenetic alopecia and gray hair

Even though both androgenetic alopecia and gray hair were not induced by COVID-19, they were both found to be risk factors for a more severe course of the infection.68-70 Most hospitalized
patients were found to have male-pattern alopecia, with a total frequency of around 70%, higher in males than in females, whose median ages were 62.5 years and 71 years, respectively.\textsuperscript{68,70} Similarly, gray hair was also found to be a severity factor in both males and females.\textsuperscript{69}

3.2 | Personal protective equipment and hygiene measures related dermatitides

Apart from the skin manifestations directly related to the virus itself, other dermatitides related to the use of PPE and to hygiene measures, as well as to the treatment of COVID-19 were reported.
3.2.1 | Types of PPE used

The most commonly used PPE was the surgical mask, but in the majority of the cases, multiple PPEs were used by the same person. The latter was more commonly applicable to healthcare workers (HCW), who also frequently wore goggles, face shields, hair caps, and gloves.71

3.2.2 | Signs, symptoms, and dermatitides secondary to PPE use and hygiene measures

Multiple studies, performed mostly through questionnaires, showed that the use of these protective equipment led to many dermatologic signs and symptoms involving the skin, the nasal mucosa, and the eyes. These include maceration, papular eruptions, erythema, burning, pruritus, dryness, and desquamation.71,72 According to one study, skin dryness affects around 68.6% of persons who wear PPEs, while facial pruritus secondary to mask use ranged between 20% and 30%, with the higher end corresponding to HCW, while the lower end corresponds to students.73 Multiple dermatitides have been seen secondary to PPE use. Among these are hand dermatitis, especially after frequent hand washing and prolonged glove wearing, delayed pressure urticaria, and hyperhidrosis.74-76 According to one report, around 74.5% of HCW developed hand dermatitis most probably secondary to latex glove wearing.77 In addition to causing the aforementioned events, PPE use was also found to exacerbate pre-existing diseases, including acne, rosacea, and seborrheic dermatitis, with acne being the most common consequence after N95 mask use.3,75,78 It even has a nomenclature, "maskne."

3.2.3 | Sites most commonly affected

The most commonly affected anatomic sites were particularly those with the greatest contact with the protective gear, with studies showing the nasal bridge and hands taking the lead, followed by the cheeks and other parts of the head and neck.72,79

3.2.4 | Risk factors

Multiple studies also concluded a relationship between duration of application of protective apparatus and the occurrence of the aforementioned signs symptoms, where a longer duration led to a higher incidence, with the average duration of 6 hours or more as a cutoff.71,72,79 One study disclosed that even after only one hour of mask wear, skin temperature and the subsequent rise in sebum secretion were increased.80 Other additional risk factors included female sex, age (young adults), severity of the epidemic in the workplace, working in a hospital (nurse, intern, resident, pharmacist), and regular hand washing, especially when it exceeded 10 times per day.79,81 Additionally, the type of mask, especially the N95 and FFP2/3 respirators led to more pressure-related symptoms than others.71
An array of skin manifestations secondary to infection with the SARS-CoV-2 virus are described, some of which are not different from those seen in other viral infections. These include the urticarial, vesicular, and erythematous eruptions. However, some skin findings were rather specific to COVID-19 infection, and not commonly seen with other viral infections, such as the chilblains described in many reports. This finding was encountered in a younger population and hypothesized to be a late manifestation of the viral infection, where the immune system targets the skin vasculature. A similarly presenting finding were the acro-ischemic lesions. Some reports considered them similar and did not differentiate between the two. In other reports, however, it was shown that acro-ischemic lesions occurred in an older population than the chilblains and portended a worse prognosis to the patients who presented with them, as compared to those who presented with chilblains. They were seen in severely ill patients, in whom D-dimer levels and prothrombin time were elevated and indicated a poorer prognosis. However, the underlying pathophysiology of such lesions could not be fully attributed to a coagulation disorder, and the possibility of a hypersensitivity reaction remains possible.

Furthermore, the underlying pathogenesis of the petechial rash in SARS-CoV-2 was described to be similar to the exanthem seen in Parvovirus B19 infection, where viral proteins in the dermal vessel wall as well as extravasated red blood cells lead to the petechial and purpuric findings.

One important syndrome to recognize is the multisystem inflammatory syndrome, that is mostly seen in children, but has also been reported in adults. Timely diagnosis of this severe syndrome is important because it affects multiple organ systems and can lead to many complications, including kidney injury, myocardial injury, hypercoagulability, and respiratory distress. It is hypothesized to be caused by a hyper-inflammatory response with cytokines II-6 and II-8 the major contributors. It was initially thought to be related to Kawasaki disease, but has recently been classified as a different novel, post-viral syndrome that is usually seen up to a month after contracting COVID-19 syndrome, regardless of whether they were symptomatic.

Moreover, despite the association of itch with multiple factors of the pandemic, including the dermatoses encountered, the psychological stress sustained, and the use of harsh chemicals and many irritants, and its substantial effect on the patients’ quality of life, the data available concerning it are still very limited.

Finally, as seen with many other viral infections and systemic illnesses, both hair and nails can be affected. A few isolated reports of nail involvement were described, and findings included leukonychia and onychomadesis, and a distinctive feature described as the red half-moon nail sign. Its underlying pathogenic mechanism is not known yet, but it has been hypothesized to be related to microvascular injury and coagulopathy.

As for the hair findings, telogen effluvium, which follows systemic stressors by 2-3 months, is an expected finding after the massive stress that patients with COVID-19 experience, on both the physiologic and the psychologic levels. However, the association of androgenetic alopecia and gray hair with a more severe course of COVID-19 infection was surprising, and it paves the way to new possibilities in treatment modalities using anti-androgens. The SARS-CoV-2 virus requires a transmembrane protein for infectivity, the transcription of which is regulated by the androgen receptor, which makes it a reasonable therapeutic, and even prophylactic option.

Nevertheless, it is to be noted that, despite the multiple skin findings that have been either hypothesized or confirmed related to COVID-19 infection, multiple characteristics of these findings are yet to be defined. For instance, prevalence studies for these findings are still missing, as well as inquiries into the underlying pathophysiology that is leading to some of these COVID-related exanthems. Additionally, many of these patients have received numerous medications and treatments, and the possibility of these treatments being a causative or exacerbating factor should be considered when applicable.

Due to the increased use of personal protective equipment and the enhanced hygiene measures, especially among healthcare workers, it is not unusual to encounter skin disorders either as a result of such habits or exacerbated by them.

Skin disorders resulting from the use of protective measures, such as gloves, goggles, and gowns, are attributed to multiple factors, including what was termed as the “hyper-hydration effect”, which was seen after prolonged wearing of the occlusive gear trapping moisture, and, along with friction, also leading to defects in skin barrier and increased susceptibility to contact dermatitis.

Excessive handwashing may also lead to irritant contact dermatitis.

An additional finding is folliculitis resulting most likely from occlusion secondary to PPE use. An important notion concerning the aforementioned mechanisms is the increase in the risk of skin damage with the increased duration of PPE use, as multiple studies have shown.

Also noted is an exacerbation of pre-existing skin diseases, with an increased rate of flares in acne, rosacea, and seborrheic dermatitis. The basis of such exacerbations might be multifactorial, including, but not limited to, an increase in psychological stress and obstruction of the skin by protective equipment use.

Lastly, considering all these findings, it is important for persons at risk, most notably healthcare workers, to follow a few instructions in order to avoid such consequences. For example, they should avoid using very hot water, refrain from prolonged glove wearing, moisturize frequently to maintain the skin barrier, and the reasonable use of alcoholic hand sanitizers.

In conclusion, during this pandemic that has affected most of the world, many skin diseases have emerged. Ranging from skin findings...
secondary to the viral infection to consequences of PPE wear and hygiene measures, as well as exacerbations of pre-existing skin diseases, these dermatological outcomes are important to be distinguished and treated for multiple reasons. First, skin findings related to the disease itself can guide us in the diagnosis, especially when other symptoms are mild. Second, skin diseases resulting from protective measures might be severe, limiting the effectiveness of the work of affected individuals, which is an undesirable outcome, especially when involving healthcare workers. Therefore, recognizing dermatological disorders resulting from this pandemic is imperative.

CONFLICT OF INTEREST

None.

ETHICAL APPROVAL

The authors confirm that the ethical policies of the journal, as noted on the journal’s author guidelines page, have been adhered to and the appropriate ethical review committee approval has been received. The US National Research Council’s guidelines for the Care and Use of Laboratory Animals were followed.

AUTHOR CONTRIBUTIONS

P.K. and J. El-K.: Conception and design. J.A., J. El-K., and A.S.: Acquisition of data. J.A., J. El-K., and A.S.: interpretation of data. J.A., J. El-K., A.S., A.B., and P.K.: Writing the manuscript. The data that support the findings of this study are available in ScholarOne data sharing field.

ORCID

Jennifer Aki  https://orcid.org/0000-0002-6728-6846
Antoine Salloum  https://orcid.org/0000-0002-7184-9859
Anthony Benedetto  https://orcid.org/0000-0002-4280-9380

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