



Review

Dermatology in a multidisciplinary approach with infectious disease and obstetric medicine against COVID-19



Rachel K. Lim BA^a, Saisanjana Kalagara MD^b, Kenneth K. Chen MD^c,
Eleftherios Mylonakis MD^b, George Kroumpouzou MD, PhD^{d,e,f,*}

^a Alpert Medical School at Brown University, Providence, Rhode Island

^b Division of Infectious Diseases, Alpert Medical School at Brown University, Providence, Rhode Island

^c Division of Obstetric and Consultative Medicine, Alpert Medical School at Brown University, Providence, Rhode Island

^d Department of Dermatology, Alpert Medical School at Brown University, Providence, Rhode Island

^e Department of Dermatology, Medical School of Jundiaí, São Paulo, Brazil

^f GK Dermatology, PC, S Weymouth, Massachusetts

ARTICLE INFO

Article history:

Received 7 May 2021

Revised 21 August 2021

Accepted 22 August 2021

Keywords:

COVID-19
skin
eruption
dermatology
infectious disease
obstetric medicine
pregnancy
vaccine

ABSTRACT

The care for patients infected with COVID-19 requires a team approach, and dermatologists may collaborate with other specialties, especially infectious disease (ID) medicine and obstetrics and gynecology (ObGyn), at every stage of the infection process. A broad spectrum of cutaneous manifestations may occur early in COVID-19 infection, making appropriate dermatologic identification critical for an early diagnosis. There is prognostic value in appropriately identifying different types of COVID-19-associated skin manifestations, which have been linked to disease severity. Such observations emanated from dermatology research, especially large series and international registries of cutaneous manifestations relating to COVID-19, and impact COVID-19 care provided by most health care providers. Also, research based on international registries of skin reactions from the COVID-19 vaccines has an impact across disciplines. An increased risk for severe illness from COVID-19 is encountered during pregnancy, and dermatologists' role is to urge ObGyn and other clinicians to monitor and educate pregnant patients about the potential for eruptions as a manifestation of COVID-19. ID and ObGyn experts indicate that teledermatology enhanced the interaction among health care providers and improved COVID-19 care. More than 40% of all dermatology consultations at a tertiary care hospital were done via teledermatology. Future collaborative research involving dermatology and specialties, such as ID and ObGyn, could help delineate guidelines for dermatology consultations in patients infected with COVID-19 and determine cases appropriate for teledermatology.

© 2021 Published by Elsevier Inc. on behalf of Women's Dermatologic Society.

This is an open access article under the CC BY-NC-ND license

(<http://creativecommons.org/licenses/by-nc-nd/4.0/>)

Contents

Introduction	641
Cutaneous manifestations related to COVID-19	641
Overview	641
Pernio-like and acral lesions	641
Maculopapular eruptions	642
Urticarial eruptions	642
Vasculitis	642
Livedo-like lesions	642
Pathophysiology of cutaneous manifestations related to COVID-19	642
Skin reactions to COVID-19 vaccines	643
Infectious disease perspectives	643

* Corresponding Author.

E-mail address: gk@gkderm.com (G. Kroumpouzou).

Obstetrics and gynecology perspectives	643
Conclusion	644
Declaration of Competing Interest	644
Funding	644
Study approval	644
References	644

What is known about this subject in regard to women and their families?

- Differences in immunological responses to COVID-19 have been observed between women and men, but whether there are sex differences in the spectrum or severity of skin eruptions associated with the disease is not yet known.
- Skin manifestations of COVID-19 can occur during pregnancy and may be the presenting sign of the disease. Early diagnosis of COVID-19 is crucial during pregnancy because of increased risk for severe disease among pregnant women and increased maternal and fetal/neonatal complications.

What is new from this article as messages for women and their families?

- There is a prognostic value in identifying different types of COVID-19 associated skin eruptions, which have been linked to disease severity.
- Although COVID-19 associated skin eruptions have been reported in pregnant patients, their prognostic value is unknown in this population.
- A multidisciplinary approach including dermatology, infectious disease medicine, and obstetrics and gynecology is essential to optimize care in many patients with COVID-19.

hypothesis that antiandrogen drugs might have a protective effect against severe COVID-19 (Goren et al., 2021). This research paves the way for future clinical research investigating antiandrogen drugs to treat COVID-19.

COVID-19 care requires a team approach, and dermatologists may collaborate with other specialties, especially infectious disease (ID) medicine and obstetrics and gynecology (ObGyn), at every stage of the infection process. Perspectives of ID experts are included in this article. ObGyn providers have collaborated with dermatologists on COVID-19 care, especially because cutaneous manifestations of COVID-19 present a diagnostic challenge in pregnant patients. In this article, we present a comprehensive overview of the dermatology contributions to COVID-19 care and research. Also, we comment on the interface and potential collaboration between dermatology and other specialties, especially ID and ObGyn, in COVID-19 care and research.

Cutaneous manifestations related to COVID-19

Overview

Soon after the spread of COVID-19 worldwide, reports of cutaneous manifestations related to the disease appeared (Recalcati, 2020). In an early study of patients with COVID-19 in Italy, 20.4% developed cutaneous manifestations, ranging from erythematous rash to widespread urticaria (Recalcati, 2020). However, in a meta-analysis, cutaneous manifestations had a prevalence rate of 5.69% among patients with COVID-19 (Rajan et al., 2020).

A broad spectrum of cutaneous manifestations has been detected in patients with COVID-19. Some of the most common manifestations include acral lesions, maculopapular eruption, and urticarial eruption. Less common manifestations include vaso-occlusive, such as fixed livedo racemosa, retiform purpura, acral ischemia, and erythema multiforme-like eruptions (Daneshgaran et al., 2020). Most manifestations precede other COVID-19 symptoms; however, chilblain-like eruption may develop late in the disease process, and vesicular and maculopapular eruptions and acral lesions may occasionally predate COVID-19 symptoms. Papulosquamous lesions last a median of 20 days, which is the longest duration of all cutaneous manifestations in a registry of cases (McMahon et al., 2021b). Pernio-like lesions last a median of 15 days. The study concluded that urticarial and morbilliform eruptions were relatively ephemeral, whereas papulosquamous and pernio-like eruptions were longer-lasting. Associations between the type of symptom and COVID-19 severity have been observed, with vasculitic (palpable purpura) and livedo racemosa-like patterns being associated with high severity and chilblain-like pattern with asymptomatic status (Marzano et al., 2021).

Pernio-like and acral lesions

There have been a large number of reports of acral pernio-like (pseudo-chilblain) lesions associated with COVID-19, especially among younger populations, unrelated to cold exposure. Pernio-like was the most frequent lesion identified (40.4% of cases) in a systematic review (Daneshgaran et al., 2020). In an international registry, pernio-like lesions accounted for 18% of cutaneous

Introduction

Dermatologists have played an important role in COVID-19 prevention and the judicious management of skin disease during this critical period (Bhargava et al., 2021c; Goldust et al., 2020a; Goren et al., 2020a). They served on the frontline in several parts of the globe (Bhargava et al., 2020b; Zheng and Lai, 2020). Most importantly, dermatologists have been focusing on demystifying skin manifestations related to COVID-19, as well as diagnosing and treating adverse effects of a plethora of drugs that have been used to treat the disease (Bhargava et al., 2021c; Galván Casas et al., 2020). Additionally, they have been involved in the management of occupational diseases caused by personal protective equipment (Bhargava et al., 2020a, 2021b; Goldust et al., 2020b). Furthermore, dermatologists have assessed the risks associated with using systemic immunosuppressants and immunomodulators for inflammatory skin disease during the pandemic (Price et al., 2020; Sadoughifar et al., 2020).

Dermatology research helped evaluate the prevalence and types of cutaneous manifestations related to COVID-19, as well as their duration and association with disease severity. The creation of international registries on skin manifestations related to COVID-19 was a major contribution (Freeman et al., 2020a; McMahon et al., 2021b). Also, dermatologists have investigated the role of androgens in COVID-19. An observational study reported that 71% of Caucasian males admitted to two Spanish hospitals for COVID-19 were diagnosed with androgenetic alopecia. This prevalence was higher than would be expected in the general population (Goren et al., 2020b). Findings of several subsequent studies led to the

manifestations among patients with laboratory-confirmed COVID-19 (Freeman et al., 2020a). In an earlier study of the same registry, pernio-like lesions accounted for 63% of dermatologic manifestations among patients with suspected or confirmed COVID-19, although most cases were in patients with suspected COVID-19 without confirmatory testing (Freeman et al., 2020b). Most pernio-like lesions occur in the feet (>80%), with smaller percentages on both the feet and hands or only the hands (Freeman et al., 2020b; Piccolo et al., 2020).

Debate exists surrounding the legitimacy of the association between acral pernio-like lesions and COVID-19. In two case series of patients presenting with pernio-like lesions during the COVID-19 pandemic, one including children only and the other adults, none of the patients tested positive for COVID-19 (Caselli et al., 2020; Herman et al., 2020). However, a case-control study comparing patients with pernio-like lesions versus controls found a significant positive odds ratio of positive IgG against the receptor-binding domain of a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein (odds ratio: 3.40; 95% confidence interval, 1.25–9.22; $p = .0162$) in cases compared with controls (Ortega-Quijano et al., 2021).

Maculopapular eruptions

Maculopapular eruptions make up to 44% of skin manifestations in an international registry of dermatologic manifestations in patients with confirmed or suspected COVID-19 (Freeman et al., 2020a). In a large Spanish cohort, patients with COVID-19 accounted for 47% of all cutaneous manifestations, but only 21.3% in a systematic review (Daneshgaran et al., 2020). Maculopapular eruptions associated with COVID-19 have been observed to follow morbilliform, purpuric, erythema multiforme-like, pityriasis rosea-like, erythema elevatum diutinum-like, and perifollicular patterns (Catala et al., 2020). Of these, generalized morbilliform eruptions have been most frequently observed (Catala et al., 2020).

Urticarial eruptions

Urticarial eruptions were first reported in relation to COVID-19 in an Italian study in which they accounted for 16.7% of skin manifestations among hospitalized patients with COVID-19 (Recalcati, 2020). In a larger study conducted in Spain, 19% of patients with suspected or confirmed COVID-19 presented with urticarial eruption (Galvan Casas et al., 2020). The presentation of urticarial eruptions is variable. In a meta-analysis including 202 cases of urticarial eruptions associated with COVID-19, the differential diagnoses included urticaria, urticarial vasculitis, idiopathic plantar hidradenitis, and neutrophilic dermatosis (Algaadi, 2020). Urticarial eruptions are mainly distributed on the trunk or in a generalized pattern, but have been also observed in facial and acral regions (Algaadi, 2020). COVID-19-associated urticarial rash has been successfully treated with antihistamines and systemic and topical steroids (Algaadi, 2020). However, COVID-19-related urticaria may be difficult to distinguish from idiopathic urticaria and urticarial eruptions triggered by other infections, foods, drugs, and emotional stress (Antia et al., 2018).

Vasculitis

Cutaneous vasculitis has been observed in patients with COVID-19, although not commonly. In an international registry of dermatologic manifestations in patients with confirmed or suspected COVID-19, palpable purpura and vasculitis accounted for 1.4% of manifestations (Freeman et al., 2020b). Several cases of cutaneous small vessel vasculitis in patients with COVID-19 have been documented, often accompanied by palpable purpura (Dominguez-

Santas et al., 2020; Mayor-Ibarguren et al., 2020; Schenker et al., 2021; Tahir et al., 2020). More specifically, leukocytoclastic vasculitis in patients with COVID-19 has been observed in both children and adults (Iraji et al., 2020; Kumar et al., 2021). Henoch-Schönlein purpura associated with COVID-19 infection has been reported (AlGhoozi and AlKhayyat, 2021).

Livedo-like lesions

Livedo-like lesions related to COVID-19 are relatively uncommon. A review study reported that vascular eruptions resembling livedo or pupura accounted for only 4% of skin manifestations and occurred mainly in elderly patients (Marzano et al., 2021). In an international registry of dermatologic manifestations in patients with confirmed or suspected COVID-19, livedo reticularis-like lesions and livedo racemosa accounted for 3.5% and 0.6% of manifestations, respectively (Freeman et al., 2020b). In a Spanish cohort, 6% of patients with suspected or confirmed COVID-19 presented with livedo-like lesions or necrosis, whereas in a French observational study, only 1 of 14 patients with COVID-19 and cutaneous symptoms displayed livedo-like lesions (Bouaziz et al., 2020; Galvan Casas et al., 2020).

Pathophysiology of cutaneous manifestations related to COVID-19

The pathologic mechanisms that cause skin lesions in patients with COVID-19 have not been adequately elucidated. To enter cells, the spike protein of SARS-CoV-2 binds to the cell membrane angiotensin-converting enzyme 2 (ACE2) receptor and the transmembrane protease serine 2 expressed on the surface of human cells (Hoffmann et al., 2020). ACE2 receptor expression has been observed in skin tissues, particularly in keratinocytes, as well as in the testes, kidneys, colon, and lungs (Xue et al., 2021). A direct pathogenic effect of SARS-CoV-2 via ACE2 receptor in the epidermis, leading to acantholysis and dyskeratosis causing visible cutaneous manifestations of infection, has been proposed (Mahe et al., 2020). Upregulation of bradykinin, a potent vasodilator typically degraded by ACE2, results in increased vascular permeability and may be involved in edematous and/or urticarial-like lesions (Kroumpouzos, 2021). Activation of bradykinin receptors that may contribute to COVID-19 disease severity and lead to inflammatory cutaneous manifestations, such as pernio-like lesions (Ehrenfeld et al., 2006; Kenne et al., 2019).

Increased vascular permeability combined with complement activation by SARS-CoV-2 could also contribute to cutaneous manifestations of COVID-19. In a case series, significant deposits of terminal complement components C5b-9, C4d, and mannose binding lectin-associated serine protease 2 consistent with sustained, systemic activation of complement pathways was observed in retiform purpura (Magro et al., 2020). Other authors suggested that an overactive immune response may be driving cutaneous manifestations of COVID-19. The release of proinflammatory cytokines, often called a cytokine storm, could reach the skin and stimulate dermal inflammatory cells, thus triggering erythematous and urticarial eruptions (Kaya et al., 2020). In a case series, robust interferon signaling and inflammation characterized by pronounced histiocytic infiltration was detected in samples of pernio-like lesions (Magro et al., 2020).

To our knowledge, sex differences in the incidence and presentation of cutaneous manifestations related to COVID-19 have not been reported. Interestingly, sex differences in the immune response to COVID-19 have been reported. In a study of patients with moderate COVID-19 who had not received immunomodulatory medications, male patients had higher plasma levels of innate immune cytokines and a more robust induction of nonclassical

monocytes, whereas female patients mounted significantly more robust T-cell activation (Takahashi et al., 2020). Also, in a prospective study of hospitalized patients with COVID-19, the levels of several cytokines, particularly IL-4, were higher in male than in female patients, but the difference did not reach significance (Petrey et al., 2021). Based on these immunologic findings, cutaneous manifestations of COVID-19 might disproportionately affect males or females, or at different points in disease progression. However, data are insufficient, and further research on sex differences in COVID-19-related cutaneous manifestations is warranted.

Skin reactions to COVID-19 vaccines

Dermatologists have studied skin reactions observed after COVID-19 vaccination that helped ease public anxiety. A major contribution was the establishment of a registry that included 414 cases of skin reactions after an mRNA vaccine (McMahon et al., 2021a). Delayed large local reactions (i.e., ≥ 4 days after the first vaccination dose) were most common, followed by local injection site reactions, urticarial eruptions, and morbilliform eruptions. Delayed large local reactions developed a median of 7 days after the first vaccine dose, primarily after the Moderna vaccine (94%), and resolved within 3 to 4 days (McMahon et al., 2021a). Forty-three percent of patients with first-dose reactions experienced a second-dose recurrence. Less common reactions included pernio/chilblains, cosmetic filler reactions, zoster, herpes simplex flares, and pityriasis rosea-like reactions. Some dermatologic reactions to mRNA vaccines, such as pernio/chilblains, mimicked SARS-CoV-2 infection itself (Lopez et al., 2021; McMahon et al., 2021a).

Most patients in the registry who developed first-dose reactions did not have a second-dose reaction, and serious adverse events (e.g., severe allergic reaction) did not develop in any patients. None of the first-dose urticaria or angioedema reports occurred on the day of vaccination; therefore, these would not be classified as immediate hypersensitivity. The presence of a cutaneous reaction to the first vaccine dose, when it appears >4 hours after injection, is not a contraindication to receiving the second dose (McMahon et al., 2021a). Most reactions resolved without medical intervention. The data provided by this dermatologist-facing registry-based study provide reassurance to clinicians tasked with counseling patients who have experienced a delayed cutaneous arm reaction after their first mRNA vaccine dose.

Infectious disease perspectives

COVID-19 is a protean disease and often requires a team approach for both the diagnosis and management of the infection and its complications. In this regard, ID physicians and dermatologists may collaborate at every stage of the infection process. Importantly, cutaneous manifestations may occur early during COVID-19 infection, making appropriate dermatologic identification critical for early diagnosis. Although most patients have cutaneous signs at the same time as or after systemic symptoms, skin manifestations can be the presenting sign of COVID-19 infection in a significant percentage of patients, as high as 10% to 17% in some reports (Galvan Casas et al., 2020; Visconti et al., 2021; Young and Fernandez 2020; Zhao et al., 2020).

Importantly, timely diagnosis of skin lesions can help with COVID-19 diagnosis and management. Consultation with dermatology is useful because COVID-19-related rashes can be similar to other viral exanthems or even medication-related reactions (Tan et al., 2021; Young and Fernandez 2020). Of note, one instructive study collected photographs of rashes from patients with a positive SARS-CoV-2 test or typical COVID-19 symptoms and had four dermatologists independently assess whether the rash was COVID-19 related. All four dermatologists agreed on the classification 82%

of the time, and three of four agreed 96% of the time, indicating high diagnostic precision among the dermatologists (Visconti et al., 2021).

There is also prognostic value in appropriately identifying different types of COVID-19-associated skin manifestations, which have been linked to disease severity (Naderi-Azad and Vender, 2021). The presence of skin findings itself does not appear correlated with severity, but there are prognostic implications with specific types of skin lesions. Vascular lesions, such as acral ischemia or livedoid eruptions, tend to affect older patients and are associated with increased intensive care unit admissions and mortality (Young and Fernandez, 2020). On the other hand, pseudo-chilblain lesions were the most common in young adults and had the highest survival rates among patients with COVID-19 and cutaneous manifestations (Galvan Casas et al., 2020; Jamshidi et al., 2021; Lai et al., 2020; Young and Fernandez 2020). Both vascular and pseudo-chilblain lesions can present on acral surfaces but are on opposite sides of the spectrum in terms of predicting disease progression and severity (Tan et al., 2021).

In addition to diagnosis and clinical evaluation, the management of skin lesions also often requires a group approach. For example, antihistamines have been used for urticaria-like lesions and systemic glucocorticoids for vascular lesions (Jamshidi et al., 2021; Rahimi and Tehraninia 2020; Tan et al., 2021). Taken in their totality, we see that due to the multi-system effects of COVID-19, a multidisciplinary approach is often needed to optimize care. In fact, patients with COVID-19 can make up a significant portion of inpatient dermatology consultations. One study found that $>30\%$ of dermatology consultations at a tertiary care hospital were for patients with COVID-19, and $>40\%$ of all dermatology consultations were done via telemedicine (Bhargava et al., 2021a; Trinidad et al., 2020; Uzuncakmak et al., 2020).

Teledermatology, which has become increasingly common since the start of the pandemic, can both increase access to dermatologic care for inpatients and reduce the risk of infection spread (Bhargava et al., 2020c; Trinidad et al., 2020). However, teledermatology has been linked to lower rates of diagnostic certainty, necessitating follow-up in-person consultations for as many as 25% of patients in one study (Rogers et al., 2021). Future research with collaboration by dermatology and ID could help further delineate guidelines for dermatology consultations in patients with COVID-19 and determine cases appropriate for teledermatology.

Obstetrics and gynecology perspectives

Pregnant women are more susceptible to viral respiratory infections due to immunologic and physiological adaptations of pregnancy (Dotters-Katz and Hughes, 2020). The influenza pandemic of 2009 showed that pregnant women experienced a higher mortality rate compared with nonpregnant women of the same age (Mosby et al., 2011). Two recently published multinational cohort studies have confirmed that COVID-19 infection during pregnancy is also associated with substantial increases in severe maternal and neonatal morbidity and mortality (Brandt et al., 2021; Villar et al., 2021). Pregnant women are at an increased risk for severe illness from COVID-19 compared with nonpregnant women due to altered physiology, increased susceptibility to infections, and compromised immunological functions during gestation (Dashraath et al., 2020). There is also an increased risk of preeclampsia, preterm birth, and other fetal complications that are possibly related to cytokine dysregulation (Alberca et al., 2020). Hence, it is most important for all clinicians who encounter pregnant women to be able to diagnose this condition promptly.

As described, cutaneous manifestations of COVID-19 infection are frequently present in our patients. It is important that there is an effective dialogue and avenue of communication between

ObGyn and dermatology because the onset of COVID-19–related cutaneous manifestations may be the earliest clue to the presence of systemic manifestations of the viral syndrome, and prompt recognition can help improve maternal and fetal outcomes in this context. Also, herpes zoster may be a sign of COVID-19 infection during pregnancy (Elsaie et al., 2020). This observation validates the link between pregnancy and a higher risk of COVID-19 complications. Dermatologists' role is to urge clinicians to monitor and educate pregnant patients about the potential for rashes, such as herpes zoster, as a symptom of COVID-19 infection.

Health care providers who care for pregnant women are accustomed to routinely examining the skin to look for signs of clinical conditions, such as viral illnesses, atopic eruption of pregnancy, polymorphic eruption of pregnancy (PEP), intrahepatic cholestasis of pregnancy, pemphigoid gestationis, and impetigo herpetiformis—a number of these skin conditions are associated with adverse maternal and especially fetal outcomes (Mehta et al., 2016). The hormonal and immune changes of gestation could affect COVID-19 cutaneous manifestations (Proietti et al., 2020). A case of PEP that developed simultaneously with SARS-CoV-2 manifestations of fever, headache, and diarrhea in a patient with COVID-19 prompted speculation that PEP could be a COVID-19 manifestation (Proietti et al., 2020). The authors suggested that a hypersensitivity reaction against viral antigens as a possible pathogenetic mechanism in their case. Erythematous and papular skin eruption associated with SARS-CoV-2 infection has been documented in a pregnant woman, but at the time of review, no case reports or studies have reported on the prognostic value of skin lesions in pregnant women with COVID-19 (Oropeza Chavez et al., 2021). Further investigation is required, and ongoing collaboration between dermatology and obstetric medicine is essential to such research.

During the ongoing COVID-19 pandemic, a number of routine clinical obstetric visits were switched to telehealth visits. This made routine examination a lot more difficult, but a number of women experienced cutaneous manifestations that were visible to the clinician via videoconferencing. On a number of occasions, dermatology expertise was sought very soon afterward to confirm whether the cutaneous manifestations were related to COVID-19. A successful collaboration between dermatology and ObGyn on a COVID-19–related eruption that presented during the immediate postpartum period was reported (Paolino et al., 2020). A number of patients also presented with unexplained cutaneous manifestations to the emergency department of the specialty maternity hospital Women & Infants of Rhode Island during the pandemic. Once again, dermatological expertise was extremely valuable in differentiating between possible COVID-19 manifestations versus other diagnoses as previously listed. Dermatology consultations helped optimize obstetric care greatly in these patients.

ObGyn providers should promptly provide the relevant obstetric or gynecological history to dermatologists to facilitate the appropriate diagnosis of a skin eruption. This is particularly useful for teledermatology consultations where the dermatologist may not have access to detailed ObGyn history data (Betancourt et al., 2020). ObGyn may also provide information about a pregnant patient's COVID-19 vaccination status, as well as any recent exposures to SARS-CoV-2, that can aid the dermatologist in establishing a diagnosis of a skin eruption.

Furthermore, ObGyn providers encounter a number of nonpregnant patients in their practice. Women with polycystic ovarian syndrome (PCOS) have an increased risk of COVID-19 infection compared with those without PCOS (Subramanian et al., 2021). The hallmarks of PCOS are insulin resistance and hyperandrogenism, and hyperandrogenic women reportedly experienced more severe COVID-19 symptoms (Cadejani et al., 2021). A possible explanation is related to hyperandrogenism, which is associated with in-

creased ACE-2 receptor expression (La Vignera et al., 2020). Nevertheless, a recent report showed no evidence of increased risk of COVID-19 infection, hospitalization, or mortality in women with acne vulgaris, PCOS, or hirsutism (Yale et al., 2021). However, the study provided no clear data on the clinical symptoms for which patients were hospitalized. Ongoing collaboration between dermatology and gynecology may provide insight into the role of sex hormones on disease incidence and severity that will contribute to a better understanding of at-risk populations (Yale et al., 2021).

Conclusion

Dermatologists have played an important role in COVID-19 prevention and the judicious management of skin disease during the pandemic. They have focused on demystifying skin manifestations related to COVID-19 infection and conducted prolific research in this field. A multidisciplinary approach with ID and ObGyn is essential to optimize care in patients with COVID-19.

Declaration of Competing Interest

The authors have no conflicts of interest. Eleftherios Mylonakis was involved in clinical trials on COVID-19. These trials were supported by Regeneron, NIH, and SciClone Pharmaceuticals, Inc. All funds were to the institution, and Eleftherios Mylonakis received no direct funds.

Funding

N/A

Study approval

N/A

References

- Alberca RW, Pereira NZ, Oliveira LMDS, Gozzi-Silva SC, Sato MN. Pregnancy, viral infection, and COVID-19. *Front Immunol* 2020;11:1672.
- Algaadi SA. Urticaria and COVID-19: A review. *Dermatol Ther* 2020;33(6):e14290.
- AIGhoozi DA, AIKhayyat HM. A child with Henoch–Schonlein purpura secondary to a COVID-19 infection. *BMJ Case Rep* 2021;14(1).
- Antia C, Baquerizo K, Korman A, Alikhan A, Bernstein JA. Urticaria: A comprehensive review: Treatment of chronic urticaria, special populations, and disease outcomes. *J Am Acad Dermatol* 2018;79(4):617–33.
- Betancourt JA, Rosenberg MA, Zevallos A, Brown JR, Mileski M. The Impact of COVID-19 on telemedicine utilization across multiple service lines in the United States. *Healthcare (Basel)* 2020;8(4):380.
- Bhargava S, Gupta M, Kroumpouzou G. Protection comes at a cost: Doctor's life inside personal protection equipment. *Dermatol Ther* 2020a;33(4):e13758.
- Bhargava S, McKeever C, Kroumpouzou G. Impact of COVID-19 pandemic on dermatology practice: Results of a web-based, global survey. *Int J Womens Dermatol* 2021a;7(2):217–23.
- Bhargava S, McKeever C, Sadoughifar R, Kroumpouzou G. Availability of personal protective equipment (PPE) among dermatologists in the COVID-19 pandemic: Assessment and risk factors in a web-based, global study. *Clin Dermatol* 2021b [Epub ahead of print].
- Bhargava S, Rokde R, Rathod D, Kroumpouzou G. Employing dermatologists on the frontline against COVID-19: All hands on deck. *Dermatol Ther* 2020b;33(5):e13420.
- Bhargava S, Sarkar R, Kroumpouzou G. Mental distress in dermatologists during COVID-19 pandemic: Assessment and risk factors in a global, cross-sectional study. *Dermatol Ther* 2020c;33(6):e14161.
- Bhargava S, Negbenebor N, Sadoughifar R, Ahmad S, Kroumpouzou G. Global impact on dermatology practice due to COVID-19. *Clin Dermatol* 2021c [Epub ahead of print].
- Bouaziz JD, Duong TA, Jachiet M, Velter C, Lestang P, Cassius C, et al. Vascular skin symptoms in COVID-19: A French observational study. *J Eur Acad Dermatol Venereol* 2020;34(9):e451–2.
- Brandt JS, Hill J, Reddy A, Schuster M, Patrick HS, Rosen T, et al. Epidemiology of coronavirus disease 2019 in pregnancy: Risk factors and associations with adverse maternal and neonatal outcomes. *Am J Obstet Gynecol* 2021;224(4):389.e1–9.

- Caselli D, Chironna M, Loconsole D, Nigri L, Mazzotta F, Bonamonte D, et al. No evidence of SARS-CoV-2 infection by polymerase chain reaction or serology in children with pseudo-chilblain. *Br J Dermatol* 2020;183(4):784–5.
- Catala A, Galvan-Casas C, Carretero-Hernandez G, Rodriguez-Jimenez P, Fernandez-Nieto D, Rodriguez-Villa A, et al. Maculopapular eruptions associated to COVID-19: A subanalysis of the COVID-Piel study. *Dermatol Ther* 2020;33(6):e14170.
- Daneshgaran G, Dubin DP, Gould DJ. Cutaneous manifestations of COVID-19: A evidence-based review. *Am J Clin Dermatol* 2020;21(5):627–39.
- Dashraath P, Wong JJ, Lim MXK, Lim LM, Li S, Biswas A, et al. Coronavirus disease 2019 (COVID-19) pandemic and pregnancy. *Am J Obstet Gynecol* 2020;222(6):521–31.
- Dominguez-Santas M, Diaz-Guimaraens B, Garcia Abellas P, Moreno-Garcia del Real C, Burgos-Blasco P, Suarez-Valle A. Cutaneous small-vessel vasculitis associated with novel 2019 coronavirus SARS-CoV-2 infection (COVID-19). *J Eur Acad Dermatol Venereol* 2020;34(10):e536–7.
- Dotter-Katz SK, Hughes BL. Considerations for obstetric care during the COVID-19 pandemic. *Am J Perinatol* 2020;37(8):773–9.
- Ehrenfeld P, Millan C, Matus CE, Figueroa JE, Burgos RA, Nualart F, et al. Activation of kinin B1 receptors induces chemotaxis of human neutrophils. *J Leukoc Biol* 2006;80(1):117–24.
- Elsaie ML, Youssef EA, Nada HA. Herpes zoster may be a marker for COVID-19 infection during pregnancy. *Cutis* 2020;106(6):318–20.
- Freeman EE, McMahon DE, Lipoff JB, Rosenbach M, Kovarik C, Desai SR, et al. The spectrum of COVID-19-associated dermatologic manifestations: an international registry of 716 patients from 31 countries. *J Am Acad Dermatol* 2020a;83(4):1118–29.
- Freeman EE, McMahon DE, Lipoff JB, Rosenbach M, Kovarik C, Takeshita J, et al. Pernio-like skin lesions associated with COVID-19: A case series of 318 patients from 8 countries. *J Am Acad Dermatol* 2020b;83(2):486–92.
- Galvan Casas C, Catala A, Carretero Hernandez G, Rodriguez-Jimenez P, Fernandez-Nieto D, Rodriguez-Villa Lario A, 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(1):71–7.
- Goldust M, Kroumpouzou G, Murrell DF, Jafferany M, Lotti T, Wollina U, et al. Use of face masks in dermatology department during the COVID-19 outbreak. *Dermatol Ther* 2020a;33(5):e13521.
- Goldust M, Kroumpouzou G, Murrell DF, Rudnicka L, Das A, Lotti T, et al. Update on COVID-19 effects in dermatology specialty. *Dermatol Ther* 2020b;33(4):e13523.
- Goren A, Rathod D, Kroumpouzou G, Jafferany M, Goldust M. Safety measures in dermatology help minimize spread of COVID-19. *Dermatol Ther* 2020a;33(4):e13773.
- Goren A, Wambier CG, McCoy J, Vano-Galvan S, Muller Ramos P. Anti-androgens may protect against severe COVID-19 outcomes: Results from a prospective cohort study of 77 hospitalized men. *J Eur Acad Dermatol Venereol* 2021;35(1):e13–15.
- Goren A, Vano-Galvan S, Wambier CG, McCoy J, Gomez-Zubiaur A, Moreno-Arrones OM, et al. A preliminary observation: Male pattern hair loss among hospitalized COVID-19 patients in Spain—A potential clue to the role of androgens in COVID-19 severity. *J Cosmet Dermatol* 2020b;19(7):1545–7.
- Herman A, Peeters C, Verroken A, Tromme I, Tennstedt D, Marot L, et al. Evaluation of chilblains as a manifestation of the COVID-19 pandemic. *JAMA Dermatol* 2020;156(9):998–1003.
- Hoffmann M, Kleine-Weber H, Schroeder S, Kruger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell* 2020;181(2):271–80 e278.
- Iraji F, Galehdari H, Siadat AH, Jazi SB. Cutaneous leukocytoclastic vasculitis secondary to COVID-19 infection: A case report. *Clin Case Rep* 2020;9(2):830–4.
- Jamshidi P, Hajikhani B, Mirsaedi M, Vahidnezhad H, Dadashi M, Javad Nasiri M. Skin manifestations in COVID-19 patients: Are they indicators for disease severity? A systematic review. *Front Med (Lausanne)* 2021;8.
- Kaya G, Kaya A, Saurat JH. Clinical and histopathological features and potential pathological mechanisms of skin lesions in COVID-19: Review of the literature. *Dermatopathology (Basel)* 2020;7(1):3–16.
- Kenne E, Rasmuson J, Renne T, Vieira ML, Muller-Esterl W, Herwald H, et al. Neutrophils engage the kallikrein-kinin system to open up the endothelial barrier in acute inflammation. *FASEB J* 2019;33(2):2599–609.
- Kroumpouzou G. Cutaneous manifestations of COVID-19: an unusual presentation with edematous plaques and pruritic, erythematous papules, and comment on the role of bradykinin storm and its therapeutic implications. *Dermatol Ther* 2021;34(2):e14753.
- Kumar G, Pillai S, Norwick P, Bukulmez H. Leucocytoclastic vasculitis secondary to COVID-19 infection in a young child. *BMJ Case Rep* 2021;14(4).
- La Vignera S, Cannarella R, Condorelli RA, Torre F, Aversa A, Calogero AE. Sex-specific SARS-CoV-2 mortality among hormone-modulated ACE-2 expression, risk of venous thromboembolism and hypovitaminosis D. *Int J Mol Sci* 2020;21(8):e2948.
- Lai CC, Ko WC, Lee PI, Jean SS, Hsueh PR. Extra-respiratory manifestations of COVID-19. *Int J Antimicrob Agents* 2020;56(2).
- Lopez S, Vakharia P, Vandergriff T, Freeman EE, Vasquez R. Pernio after COVID-19 vaccination. *Br J Dermatol* 2021;185(2):445–7.
- Magro C, Mulvey JJ, Berlin D, Nuovo G, Salvatore S, Harp J, et al. Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: A report of five cases. *Transl Res* 2020;220:1–13.
- Mahe A, Birckel E, Merklen C, Lefebvre P, Hannedouche C, Jost M, et al. Histology of skin lesions establishes that the vesicular rash associated with COVID-19 is not 'varicella-like'. *J Eur Acad Dermatol Venereol* 2020;34(10):e559–61.
- Marzano AV, Genovese G, Moltrasio C, Gaspari V, Vezzoli P, Maione V, et al. The clinical spectrum of COVID-19-associated cutaneous manifestations: An Italian multicenter study of 200 adult patients. *J Am Acad Dermatol* 2021;84(5):1356–63.
- Mayor-Ibarguren A, Feito-Rodriguez M, Quintana Castanedo L, Ruiz-Bravo E, Montero Vega D, Herranz-Pinto P. Cutaneous small vessel vasculitis secondary to COVID-19 infection: A case report. *J Eur Acad Dermatol Venereol* 2020;34(10):e541–2.
- McMahon DE, Amerson E, Rosenbach M, Lipoff JB, Moustafa D, Tyagi A, et al. Cutaneous reactions reported after Moderna and Pfizer COVID-19 vaccination: A registry-based study of 414 cases. *J Am Acad Dermatol* 2021a;85(1):46–55.
- McMahon DE, Gallman AE, Hruza GJ, Rosenbach M, Lipoff JB, Desai SR, et al. Long COVID in the skin: A registry analysis of COVID-19 dermatological duration. *Lancet Infect Dis* 2021b;21(3):313–14.
- Mehta N, Chen KK, Kroumpouzou G. Skin disease in pregnancy: The approach of the obstetric medicine physician. *Clin Dermatol* 2016;34(3):320–6.
- Mosby LG, Rasmussen SA, Jamieson DJ. 2009 pandemic influenza A (H1N1) in pregnancy: A systematic review of the literature. *Am J Obstet Gynecol* 2011;205(1):10–18.
- Naderi-Azad S, Vender R. Lessons from the first wave of the pandemic: Skin features of COVID-19 can be divided into inflammatory and vascular patterns. *J Cutan Med Surg* 2021;25(2):169–76.
- Oropeza Chavez L, Sanchez Tinajero A, Martinez Orozco JA, Becerril Vargas E, Dolores De la Merced AD, Ruiz Santillan DP, et al. A 34-year-old woman with a diamniotic dichorionic twin pregnancy presenting with an erythematous and papular skin rash associated with SARS-CoV-2 infection. *Am J Case Rep* 2021;22.
- Ortega-Quijano D, Fernandez-Nieto D, Jimenez-Cauhe J, Cortes-Cuevas JL, Marcos-Mencia D, Rodriguez-Dominguez M, et al. Association between COVID-19 and chilblains: A case-control study. *J Eur Acad Dermatol Venereol* 2021;35(6):e359–61.
- Paolino G, Canti V, Mercuri SR, Rovere Querini P, Candiani M, Pasi F. Diffuse cutaneous manifestation in a new mother with COVID-19 (SARS-Cov-2). *Int J Dermatol* 2020;59(7):874–5.
- Petrey AC, Qeadan F, Middleton EA, Pinchuk IV, Campbell RA, Beswick EJ. Cytokine release syndrome in COVID-19: Innate immune, vascular, and platelet pathogenic factors differ in severity of disease and sex. *J Leukoc Biol* 2021;109(1):55–66.
- Piccolo V, Neri I, Filippeschi C, Oranges T, Argenziano G, Battarra VC, et al. Chilblain-like lesions during COVID-19 epidemic: A preliminary study on 63 patients. *J Eur Acad Dermatol Venereol* 2020;34(7):e291–3.
- Price KN, Frew JW, Hsiao JL, Shi VY. COVID-19 and immunomodulator/immunosuppressant use in dermatology. *J Am Acad Dermatol* 2020;82:e173–5.
- Proietti I, Bernardini N, Tolino E, Mambrin A, Balduzzi V, Marchesiello A, et al. Polymorphic eruption of pregnancy as a possible COVID-19 manifestation. *Dermatol Ther* 2020;33(6):e14117.
- Rahimi H, Tehranchinia Z. A comprehensive review of cutaneous manifestations associated with COVID-19. *Biomed Res Int* 2020;2020.
- Rajan MB, Kumar MP, Bhardwaj A. The trend of cutaneous lesions during COVID-19 pandemic: Lessons from a meta-analysis and systematic review. *Int J Dermatol* 2020;59(11):1358–70.
- Recalcati S. Cutaneous manifestations in COVID-19: A first perspective. *J Eur Acad Dermatol Venereol* 2020;34(5):e212–13.
- Rogers MC, Wallace MM, Wheless L, Dewan AK. Impact of the COVID-19 pandemic on inpatient dermatology consult patterns at a tertiary care hospital: A retrospective cohort study. *J Am Acad Dermatol* 2021;84(1):156–8.
- Sadoughifar R, Goldust M, Kroumpouzou G, Szepletowski JC, Lotti T, Sandhu S. Dermatologic treatments in the era of COVID-19 pandemic—Data and hypothesis. *Dermatol Ther* 2020;33(4):e13562.
- Schenker HM, Hagen M, Simon D, Schett G, Manger B. Reactive arthritis and cutaneous vasculitis after SARS-CoV-2 infection. *Rheumatology (Oxford)* 2021;60(1):479–80.
- Subramanian A, Anand A, Adderley NJ, et al. Increased COVID-19 infections in women with polycystic ovary syndrome: A population-based study. *Eur J Endocrinol* 2021;184(5):637–45.
- Tahir A, Sohail Z, Nasim B, Parmar NV. Widespread cutaneous small vessel vasculitis secondary to COVID-19 infection. *Int J Dermatol* 2020;59(10):1278–9.
- Takahashi T, Ellingson MK, Wong P, Israelov B, Lucas C, Klein J, et al. Sex differences in immune responses that underlie COVID-19 disease outcomes. *Nature* 2020;588(7837):315–20.
- Tan SW, Tam YC, Oh CC. Skin manifestations of COVID-19: A worldwide review. *JAAD Int* 2021;2:119–33.
- Trinidad J, Kroshinsky D, Kaffenberger BH, Rojek NW. Telemedicine for inpatient dermatology consultations in response to the COVID-19 pandemic. *J Am Acad Dermatol* 2020;83(1):e69–71.
- Uzunackmak TK, Bayazit S, Askin O, Engin B, Kutlubay Z. Inpatient dermatology consultations during COVID 19 pandemic in a tertiary referral center. *Dermatol Ther* 2020;33(6):e13883.
- Villar J, Ariff S, Gunier R, Thiruvengadam R, Rauch S, Kholin A, et al. Maternal and neonatal morbidity and mortality among pregnant women with and without COVID-19 infection: The INTERCOVID Multinational Cohort Study. *JAMA Pediatr* 2021;175(8):817–26.
- Visconti A, Bataille V, Rossi N, Kluk J, Murphy R, Puig S, et al. Diagnostic

- value of cutaneous manifestation of SARS-CoV-2 infection. *Br J Dermatol* 2021;184(5):880–7.
- Xue X, Mi Z, Wang Z, Pang Z, Liu H, Zhang F. High Expression of ACE2 on keratinocytes reveals skin as a potential target for SARS-CoV-2. *J Invest Dermatol* 2021;141(1):206–9 e201.
- Yale K, Isanadi R, Ghigi A, Zheng K, Goren A, Mesinkovska NA. Androgens and women: COVID-19 outcomes in women with acne vulgaris, polycystic ovarian syndrome, and hirsutism. *Int J Dermatol* 2021;60(7):e267–8.
- Young S, Fernandez AP. Skin manifestations of COVID-19. *Cleve Clin J Med* 2020 [Epub ahead of print].
- Zhao Q, Fang X, Pang Z, Zhang B, Liu H, Zhang F. COVID-19 and cutaneous manifestations: A systematic review. *J Eur Acad Dermatol Venereol* 2020;34(11):2505–10.
- Zheng Y, Lai W. Dermatology staff participate in fight against Covid-19 in China. *J Eur Acad Dermatol Venereol* 2020;34:e210–11.