

REVIEW ARTICLE

Challenges of COVID-19 pandemic for dermatology

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a new coronavirus responsible for the pandemic named coronavirus disease 2019 (COVID-19). The disease causes SARS with a significant morbidity and mortality. We provide a review with a focus on COVID-19 in dermatology. We discuss triage of suspected infectious patients, protection of medical doctors and nurses. We discuss the available data on cutaneous symptoms, although disease-specific symptoms have yet not been observed. COVID-19 is a challenge for the treatment of dermatologic patients, either with severe inflammatory disorders or with skin cancer. The consequences for systemic treatment are obvious but it will be most important to collect the clinical data for a better decision process. Last but not least, education in dermatology for students will not be temporarily possible in the classical settings. COVID-19, although not a skin disease, by itself has an immense impact on dermatology.

KEYWORDS

COVID-19 pandemic, dermatology, SARS-CoV-2

1 | INTRODUCTION

The outbreak of a newly recognized coronavirus in Central China, province Hubei, in December 2019 marked the beginning of a new pandemic named coronavirus disease 2019 (COVID-19). COVID-19 is caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is structurally related to two other coronaviruses that caused SARS and Middle East respiratory syndrome. Coronaviruses are enveloped, positive single-stranded large RNA viruses. SARS-CoV-2 belongs to the beta subgroup, which is known to be capable of causing severe disease and fatalities with respiratory and fecal-oral infectivity.¹

Among the initial 425 patients with confirmed COVID-19-induced pneumonia, the median age was 59 years. The mean incubation period was 5.2 days, with the 95th percentile of the distribution at 12.5 days. The estimated basic reproduction number R_0 was 2.2 for Hubei. The mean interval between outbreak of the disease and hospitalization was 9.1 to 12.5 days.² Until February 26, 2020, more than 78 000 laboratory-confirmed cases had been recorded in China.³

Additional hot spots of the pandemic are the United States (>500 000), Spain, Italy, and Germany (each with >100 000)

registered infections, but the number infections of is increasing worldwide with about 1.8 million cases worldwide on April 12, 2020.⁴

Mucosal membranes are the major entry point for an infection with the new coronavirus. On biopsies of fresh cases, COVID-19-induced vascular changes have also been demonstrated in internal organs and the skin but not the virus itself.⁵

Specific cutaneous manifestations of COVID-19 infection, however, have not been described so far.³

2 | PREVENTION OF INFECTION IN DERMATOLOGY

Triage of patients with suspected infection is important at hospitals. The diagnosis of COVID-19 is mainly made on clinical signs such as fever, fatigue, dry cough, pneumonia, headache, diarrhea, hemoptysis, dyspnea, rhinorrhea, and on radiological findings. Laboratory tests can confirm diagnosis.⁶

The hospital has to reorganize activities in dermatology, with a strict focus on emergency patients and cancer patients for primary tumor surgery. Inpatient beds, outpatient consultations, and staff are

reduced. Dermatologists support triage of patients in the corona ambulance.⁷

Persistence of coronaviruses on inanimate surfaces like plastic, metal, or glass had been observed for up to 9 days. Surface disinfection with ethanol (62%-71%), 0.1% sodium hypochloride, or 0.5% hydrogen peroxide can effectively inactivate these virus particles within 1 minute.⁸

Doctors and nurses need to be protected. Sanitary masks and goggles reduce the risk of viral transmission. This is in particular of importance in clinical dermatology, since clear dermatological diagnoses can rarely be done from a distance larger than 20 cm. If we think of dermoscopy, the distance will be much smaller. Hand washes and disinfection with alcoholic solutions are part of the preventive measures when dealing with patients in dermatology.⁹ Enveloped viruses like SARS-CoV-2 respond better to ethanol than propanol. Minimal contact time is 30 seconds. The addition of other antimicrobial compounds to alcoholic hand disinfections does not increase efficacy but may increase the risk of irritant contact dermatitis. Alcoholic hand disinfectants preserve the epidermal barrier better than hand washes with soap.¹⁰

Disinfection of the medical staff is recommended before and after direct contact to a patient, before any aseptic procedure, after potential exposure to body fluids, and after direct contact to potentially contaminated items or surfaces.¹¹

Structural and organizational measures are also needed, in particular in hospitals with interdisciplinary activities such as tumor boards, councils, and emergency departments.¹²

The personal protective equipment, however, can cause skin disorders and/or aggravate preexisting skin disease. Facial inflammatory papules have been noted after prolonged wearing protective goggles. Acne and aggravation of rosacea, seborrheic dermatitis, and facial itching could occur.^{11,13}

The combination of a paper towels with the facial mask has been recommended to reduce moisture when wearing the mask.¹⁴

Delayed pressure urticaria is possible after wearing goggles and masks to tight.¹¹ Hyperhidrosis has been reported in two-third of Chinese health care workers involved in care for COVID-19 patients.¹¹ This may result in a higher risk for nondiphtheroid corynebacterial disorders, other bacterial infections, and tinea.¹⁵

Intensified handwashing and disinfection can cause irritant contact dermatitis by interrupting the epidermal barrier functions. As in other areas of occupational dermatology, the use of disinfectants alone is better tolerated than the combination of soap and disinfectant. Protective creams before the shift and moisturizers during the day reduce the risk of occupational hand dermatitis.^{9,11}

Protective gloves are part of the personal protection. Hands should be clean, disinfected, and dry before wearing the gloves. Long-term use of gloves can cause hyperhidrosis and hyperhydration of the horny layer. Disturbances of epidermal barrier function, maceration, and erosion of skin are possible consequences. This will also increase the risk for allergic contact dermatitis. After changing gloves, a hand wash is recommended followed by a skin care product.¹¹

A recent study among 542 doctors and nurses of tertiary hospitals involved in COVID-19 patient care in Hubei, China, underlined the dimension of occupational skin diseases. The general prevalence rate of occupational skin damages was 97.0% (526/542) among first-line health care workers. The nasal bridge was the most commonly affected site (83.1%). Cheeks, hands, and forehead were also affected. The risk increased if personal protective equipment was carried over 6 hours. The combination of frequent (>10 times/d) hand hygiene and longer time of gloves wearing lead to an odds ratio of 2.17 for occupational hand dermatitis.¹²

Another survey among 376 health care workers of university and regional hospitals in the province of Wuhan, China, reported skin problems in 74.5%. Hands were affected in 84.5%, followed by cheeks and nasal bridge. Clinical signs were xerosis, eczematous lesions, and maceration. Despite the increased frequency of handwashing and disinfection, only 22.1% used regularly moisturizers.¹⁶

Hot water for hand wash and alkaline soaps increases the risk of occupational hand dermatitis.¹⁷

There is an excellent Cochrane Review on interventions for preventing occupational hand dermatitis that can be used as guidance.¹⁸ The authors come to the conclusion that moisturizers alone or in combination with barrier creams may result in a significant improved protection in both the short-term and in the long-term perspectives. If this can also reduce the incidence of occupational irritant hand dermatitis remains to be confirmed.

Special guidelines for dermoscopy in the pandemic have been suggested recently. They include reduction of dermoscopy in dermatology practice, selection of patients, disinfection of body area and dermatoscope, patient and doctor wearing facial masks, and protective covers for the dermatoscope.¹⁹

3 | GENERALIZED CUTANEOUS ERUPTIONS WITH FEVER AND OTHER CUTANEOUS MANIFESTATIONS

It has been shown that cancer patients and patients under immunosuppression belong to a high-risk group for COVID-19. These are patients with a variety of medical drugs that may induce generalized drug eruptions.

COVID-19 patients may be treated with antibiotics and antiviral substances that may cause drug eruptions as well. Drug-related eosinophilia with systemic symptoms is an important differential diagnosis.²⁰ Furthermore, several viral infections like measles, dengue fever, rubella can cause generalized cutaneous eruptions with fever.²¹

Zhang et al²² reported that lymphopenia (75.4%) and eosinopenia (52.9%) were observed commonly among their 140 patients. Drug hypersensitivity (11.4%) and urticaria (1.4%) were the most frequent cutaneous symptoms.²²

A report from Italy found cutaneous symptoms in 18 of 88 patients in intense care unit (ICU) such as erythematous rash (n = 14), widespread urticaria (n = 3), and chickenpox-like vesicles (n = 1).²³ In this investigation, no confirmation of diagnosis by

histopathology was possible. The diagnoses were only clinical. In our hospital, cutaneous symptoms had not been observed.

The dermatologist is challenged to differentiate the various types (infectious, allergic) of generalized rash with fever.²⁴ Furthermore, noninfectious, nonallergic diseases like miliaria rubra may be seen in patients on the ICU with and without fever.²⁵

We need more data on possible cutaneous manifestations of COVID-19 and we need a confirmation of diagnoses. Are COVID-19 patients at a higher risk of drug-related skin disease? Honestly, we do not know yet.

Among COVID-19 patients on ICU disseminated intravascular coagulation (DIC) has been observed, which leads to acral ischemia and dry gangrene. Treatment with low-molecular-weight heparin was of limited value. DIC is a risk factor for a fatal outcome, since five of seven reported patients died with 12 days after confirmed diagnosis.²⁶

Aggravation of preexisting skin disease such as atopic dermatitis, psoriasis, and rosacea has been observed in some COVID-19 patients. Emotional tension has been considered a major contributing factor.¹³

4 | SYSTEMIC MEDICAL THERAPY FOR INFLAMMATORY SKIN DISEASE

Moderate-to-severe psoriasis can be treated by classical systemic drugs such as methotrexate, ciclosporin A, fumaric esters, and variety of targeted treatments with biologicals and small molecules. Patients suffering from psoriasis arthritis, moderate-to-severe hidradenitis suppurativa, or atopic dermatitis benefit from modern systemic treatments as well. Should patients on these drugs interrupt their treatment?

Data are sparse on the subject, but there seems to be consensus that patients with a need for systemic drug therapy and no clinical symptoms of COVID-19 should better continue their treatment instead of risking severe flares. The Australia/New Zealand consensus statement framed: "There is currently insufficient evidence to determine whether dermatology patients on systemic immunomodulators are at increased risk of developing COVID-19 infection or more likely to have severe disease...."²⁷

Systemic corticosteroids are not recommended in acute COVID-19, since doses ≥ 20 mg/d are immunosuppressive and may prolong the viral shedding.²⁸

Among the biologicals, the theoretical risk of COVID-19 infection seems to be higher with inhibitors of tumor necrosis factor alpha (TNF- α) compared to interleukin (IL) inhibitors. Among the TNF- α , the risk seems to be somewhat increased with infliximab and its biosimilars. In general, TNF- α is not recommended during infectious disease.²⁹

Ustekinumab, risankizumab, ixekizumab, and brodalumab do not increase the risk of respiratory infections in general.^{30,31} However, the data should be interpreted with caution, since we do not have the data for COVID-19 yet.

There are reports on drug-induced interstitial lung disease by infliximab, adalimumab, and ustekinumab.³² Patients with preexistent pulmonary problems have a higher risk for COVID-19.

IL-17 plays an important role in mucosal protection against bacteria and fungi by the recruitment of neutrophils and induction of antimicrobial peptides. Aberrant expression of IL-17 is associated to cystic fibrosis, pulmonary hypersensitivity, asthma, and lung fibrosis.³³ It has been demonstrated that two other SARS viruses, that is, human betacoronavirus 2c Erasmus Medical Center (HCoV-EMC) and SARS-CoV, upregulate the IL-17-related pathway in lung epithelial cells.³⁴ Theoretically, IL-17 inhibitors might reduce the IL-17 dependent SARS-induced cytokine storm. Therefore, IL-17 inhibitors seem to be safer than TNF- α for psoriasis during the pandemic.

What do we know about IL-12/IL-23 inhibitors? SARS-CoV-transfected lung cancer cells do not overexpress IL-23 and IL-12p40, and infected dendritic cells had lower expression of IL-12p40 than controls.^{34,35} Severe SARS-CoV-2 infection leads to increased expression of TNF- α , IL-1, IL-6, and IL-8.^{36,37} Under these circumstances, IL-12/IL-23 inhibitors do not seem to be beneficial for COVID-19 patients.³⁸

Last but not least, in COVID-19 patients, there is a moderate increase of TNF- α in severe infections has been observed. This would argue for some benefit of TNF- α in such patients. Indeed, a randomized, controlled trial of adalimumab for COVID-19 has been registered (ChiCTR2000030089).³⁷

The indication for initiation of systemic drug therapy in psoriasis should be seen more critical during the pandemic. Perhaps, there is a better time to start with the new drugs than just now.³⁹ Similar considerations pertain for patients with moderate-to-severe atopic dermatitis and hidradenitis suppurativa.

The European Task Force on Atopic Dermatitis recommended:

- To continue all immune-modulating treatments, including immune-suppressive therapy, since exacerbations of underlying diseases can have a large negative impact on patient's immunity.
- To strictly follow the recommendations for patients at risk issued by the local health authorities in each European country.
- To carefully observe hygienic procedures using hand wash and disinfectants. Nonirritant soap substitutes should be used in the same way as directed for soap. Moisturizers should be applied afterwards.⁴⁰

For patients with COVID-19 infection, an interdisciplinary risk assessment is recommended. Considering severity of the disease and comorbidities such as asthma, chronic obstructive lung disease, and other immune-modulating treatment might be continued or paused in accordance with current guidelines on active infections and systemic therapy.⁴⁰

For Australia and New Zealand, an "immediate withheld" of all immunomodulators, "with the possible exception of corticosteroid therapy" has been recommended for patients with suspected or confirmed COVID-19 infection.²⁷

5 | COVID-19 AND THE SKIN CANCER PATIENT

Nonmelanoma skin cancer is the most frequent malignancy. Surgery of primary tumors should not be delayed, in particular in critical

topographical areas, such as perioral, periocular. Will the limitation of personal protection equipment (PPE) result in a prioritization of cancer and COVID-19 patients?

Malignant melanoma is more aggressive. The best curative treatment is the early complete surgical removal. In case of metastatic disease, systemic treatment has become increasingly effective with a significant prolongation of survival for responders. In patients with metastatic melanoma, treatment delay may result in a loss of the window to treat. For solid tumor patients, “adjuvant therapy with curative intent likely should proceed” according to Ueda et al.⁴¹

Palliative care will play a greater role in terminally ill skin cancer patients who may acquire COVID-19 infection, since their chance to survive the infection is minimal even with all available equipment of an ICU.⁴²

6 | TEACHING DERMATOLOGY

Many universities have been closed during the COVID-19 pandemic. Social distancing forbids classical lectures, seminars, and bedside teaching. Digital tools like www.cyberderm.net may offer a way to continue teaching dermatology to students. Teledermatology may temporarily substitute bedside teaching.⁴³

7 | CONCLUSIONS

Dermatology and dermatologists cannot stand off the COVID-19 pandemic. They must be prepared. Dermatologists are important in preventive measures of the health care staff and in the differential diagnosis of generalized rash with fever. Dermatologists need to give advice for patients with severe inflammatory skin disease and systemic drug therapy. Ethical care for advanced skin cancer patients is another challenge. But we are faced to a global problem with a number of unknown facts what does not ease our decisions.⁴⁴

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

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