

Review Article

Unveiling the dermatological manifestations of nCOVID-19

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Received: 13 April 2020

Revised: 22 April 2020

Accepted: 24 April 2020

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ABSTRACT

Coronaviruses are RNA viruses that have become a major public health concern since the severe acute respiratory syndrome CoV (SARS-CoV-2) outbreak in 2002. The continuous evolution of coronaviruses was further highlighted with the emergence of the middle east respiratory syndrome CoV (MERS-CoV) outbreak in 2012. The spike glycoprotein of SARS-CoV-2 plays a pivotal role in the entry of virus into the cell and it further interacts with ACE-II receptors which are widely distributed on the human cell surface especially on alveolar type II cells (AT-2) and endothelium. Currently, the world is concerned about the 2019 novel CoV (SARS-CoV-2) that was initially identified in the city of Wuhan, China in December 2019. Patients presented with severe viral pneumonia and respiratory illness. Despite the virus not being dermatotropic, several skin conditions have emerged mainly as a result of prolonged contact with personal protective equipment and excessive personal hygiene. In this review, we discuss structure, genome organisation, entry of CoVs into target cells, probable cutaneous manifestation that dermatologists may be aware of skin complications and the preventive measures, outcome of the disease and the management.

Keywords: Coronavirus, nCOVID-19, Dermatotropic, Viral pneumonia

INTRODUCTION

Coronaviruses continue to pose serious health threats to humans and those animals adducing for their zoonotic origin. From 2002 to 2003, severe acute respiratory syndrome coronavirus (SARS-CoV-2) infected 8,000 people, with a fatality rate of 10%.^{1,2} Since 2012, Middle East respiratory syndrome coronavirus (MERS-CoV) had infected >1,700 people, with a fatality rate of 36% respectively.^{3,4} Since 2013, porcine epidemic diarrhoea coronavirus (PEDV) had swept throughout the United States, causing an almost 100% fatality rate in piglets and wiping out more than 10% of America's pig population in less than a year.⁵⁻⁷ In general, coronavirus caused

widespread respiratory, gastrointestinal, and central nervous system diseases in humans and other animals accounting for huge loss of lives and economy globally.^{8,9} These viruses have high mutational characterization which facilitates adaption to new environments relatively with ease. Further to add on; they efficiently alter the host range and tissue tropism to shed their infectivity.^{10,11} Therefore, coronaviruses can be regarded as biological weapon posing constant and long-term health threats to humanity. Coronaviruses were discovered in the 1960s and they were classified under the family Coronaviridae, which is the largest family within the order Nidovirales (Figure 1).¹²⁻¹⁶ nCOVID-19 are typically harboured in mammals and birds and are common in camels, cattle, cats, bats, and other animals.¹³

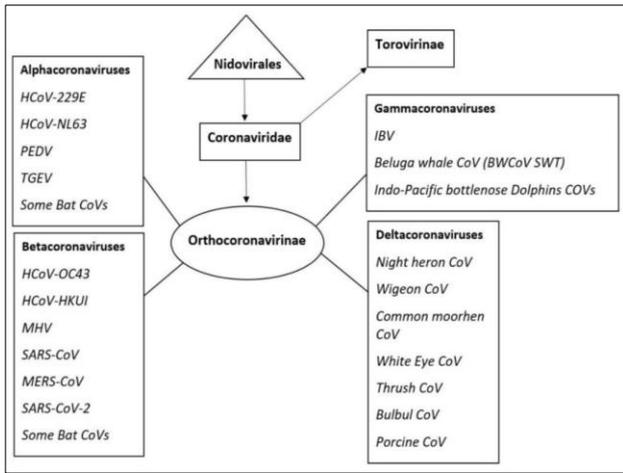


Figure 1: Classification of different types of coronaviruses.¹⁶

VIRION STRUCTURE AND FUNCTION

Coronaviruses (nCOVID-19/SARS-CoV-2) are enveloped viruses with round or pleomorphic structure of approximately 80 nm to 120 nm in diameter containing positive single stranded RNA genome of 30 kb size.^{17,18} This genome is complexed with basic nucleocapsid protein (N) to form a helical viral protein and these are the spike proteins (S) which are type-I glycoprotein that forms the peplomers on the virion surface giving it a crown-like structure (as shown in Figure 2).¹⁹ The membrane protein (M) which spans three times the viral membrane has a short N-terminal ectodomain and a cytoplasmic tail. The small membrane protein (E) is found to be highly hydrophobic and this spans twice the viral membrane which has both N and C terminals on the interior part of the virion.^{20,21} For all coronaviruses, the structural proteins are encoded in order of S-E-M-N within one third of the genome and each group of coronaviruses encodes a group of unique small proteins which are non-essential proteins and are found to serve as accessory proteins to interact or interfere with the host innate immune responses which has not been demonstrated for any of these proteins.^{22,23}

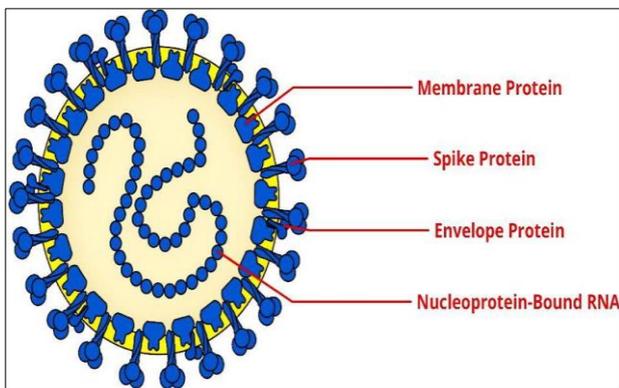


Figure 2: Structure of nCOVID-19 (SARS-CoV-2).¹⁹

Genome organization and replication

The RNA genome of nCOVID-19 is the second largest of all RNA viruses, which ranges from 26 to 32 kilo-bases (kb) in size.²⁴ Viral RNA codes for structural and nonstructural proteins.²⁵ The structural proteins together with a few nonstructural proteins, with different functions, are coded within the 3' end of the viral genome.²⁶ However, the 5' two-thirds of the genome codes for nonstructural proteins that are important in viral replication, including the RNA dependent RNA polymerase (RdRP).²⁵ Once the viral genome is inside the host cell cytoplasm following viral entry, translation of the 5' end of viral RNA produces the RdRP, which uses viral RNA as a template to generate virus specific mRNAs (subgenomic mRNAs) from subgenomic negative strand intermediates.^{26,27} Translation of subgenomic mRNAs leads to the production of structural and nonstructural viral proteins.²⁵ Once sufficient structural proteins and genomic viral RNA are formed, viral RNA is then assembled with viral structural proteins into virions. Viral assembly and budding occur in smooth walled vesicles in the endoplasmic reticulum–Golgi intermediate compartment (ERGIC).²⁵

ORIGIN AND TRANSMISSION

The SARS-CoV-2 is a β -coronavirus, which is enveloped non-segmented positive-sense RNA virus (subgenus *Sarbecovirus*, Orthocoronavirinae subfamily).²⁸ Coronaviruses (nCoVID) are divided into four genera, including α -/ β -/ γ -/ δ -CoV. α - and β -CoV are able to infect mammals, while γ - and δ -CoV tend to infect birds. Previously, six CoVs have been identified as human-susceptible virus, among which α -CoVs HCoV-229E and HCoV-NL63, and β -CoVs HCoV-HKU1 and HCoV-OC43 with low pathogenicity, cause mild respiratory symptoms similar to a common cold, respectively. The other two known β -CoVs, SARS-CoV and MERS-CoV lead to severe and potentially fatal respiratory tract infections.²⁹ It was found that the genome sequence of SARS-CoV-2 is 96.2% identical to a bat CoV RaTG13. It is suspected that bat is a natural host of virus origin, and SARS-CoV-2 might be transmitted from bats via unknown intermediate hosts to infect humans, based on virus genome sequencing results and evolutionary analysis. It is clear now that SARS-CoV-2 could use angiotensin-converting enzyme 2 (ACE2), the same receptor as SARS-CoV-2 to infect humans (as shown in Figure 3).^{30,31}

CLINICAL CHARACTERISTICS

As an emerging acute respiratory infectious disease, nCOVID-19 primarily spreads through the respiratory tract, by droplets, respiratory secretions, and direct contact for a low infective dose.^{32,33} Otherwise, it has been reported that SARS-CoV-2 was isolated from fecal swabs of a severe pneumonia patient on 10 February 2020 from a critical case in the Fifth Affiliated Hospital,

Sun Yat-Sen University, Guangdong, China. Zhang et al have found the presence of SARS-CoV-2 in fecal swabs and blood, indicating the possibility of multiple routes transmission.³⁴ ACE2 protein is abundantly present on lung alveolar epithelial cells and enterocytes of small intestine, which may help understand the various routes of infection and disease manifestations.³⁵ The incubation period of nCOVID-19 is 1–14 days (mostly 3–7 days),

and is contagious during the latency period based on the current epidemiological investigation.³⁶ It affects people of all ages. However, older persons, those with underlying chronic medical conditions, and those who are immunosuppressed have a higher risk of developing severe, life threatening illness.³⁷ Also, young and otherwise healthy people can become very sick and may die.

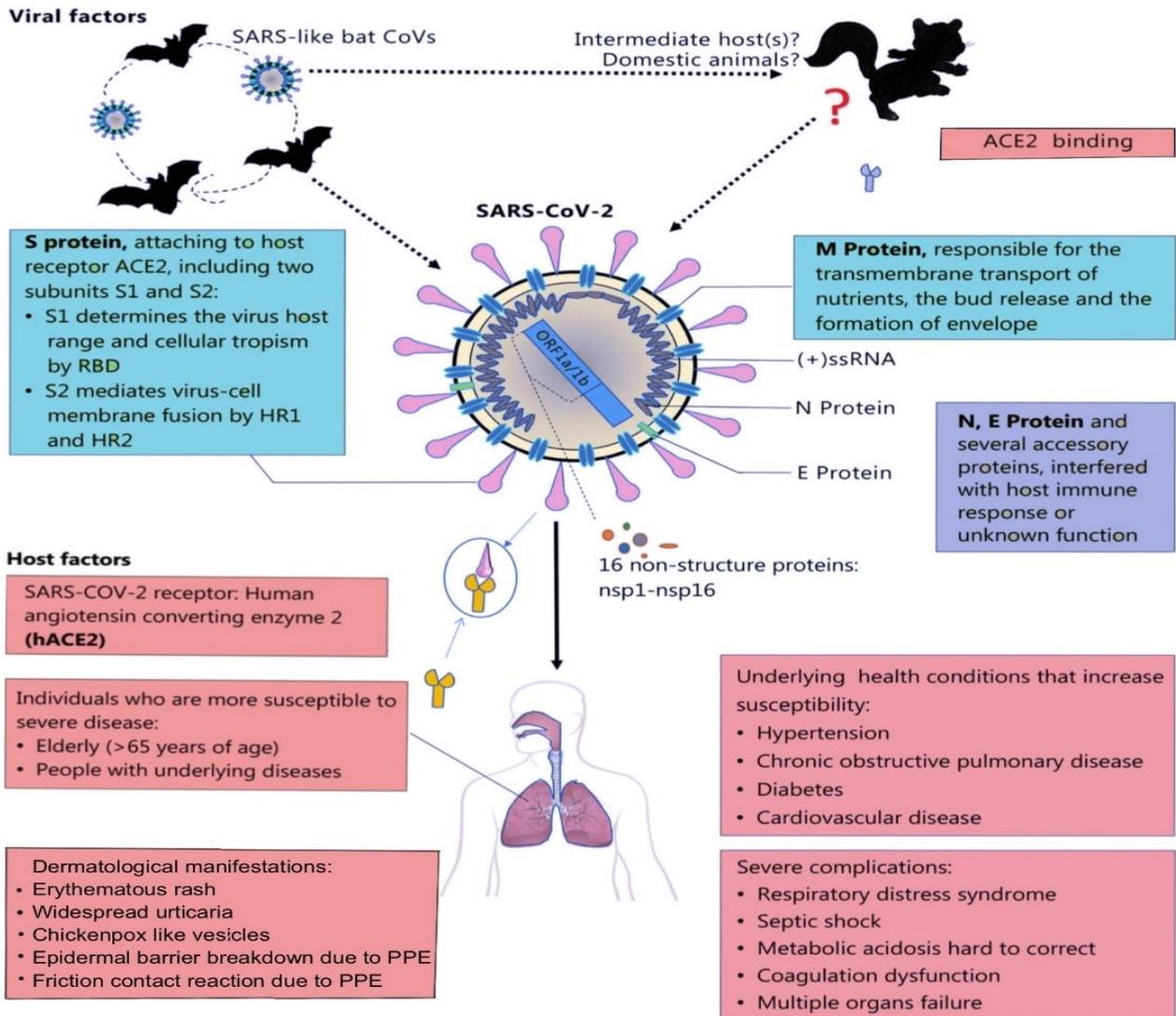


Figure 3: Pathogenesis of SARS-CoV-2.³¹

In a study conducted by Guan et al, the median age of patients was 47 years, and 41.9% of patients were females.³⁸ As it is designated SARS-CoV-2, nCOVID-19 patients presented certainly similar symptoms, such as fever, malaise, and cough.³⁹ Most adults and children with SARS-CoV-2 infection presented with mild flu-like symptoms and a few patients were in critical condition and rapidly developed acute respiratory distress syndrome, respiratory failure, multiple organ failure, even deaths.⁴⁰

From nanometers to meters: How coronavirus affects the largest organ of the body

The cutaneous manifestations of nCOVID-19 are rare, but still, no other disease has ever had a profound effect on dermatologists and their practices. Though it was depicted that the infection involves changes of the heart, vasculature, liver and kidney, the typical skin pattern was not initially observed. Subsequently, mucosal membranes have been identified as the most common entry for the infection which includes the conjunctiva with the otic

canal having the lowest risk of transmission. Specific skin changes due to nCOVID-19 infection have been described and could be due to iatrogenic secondary involvement of the skin.⁴¹ The skin manifestations of nCOVID-19 infection were shown in Figure 4a-f.

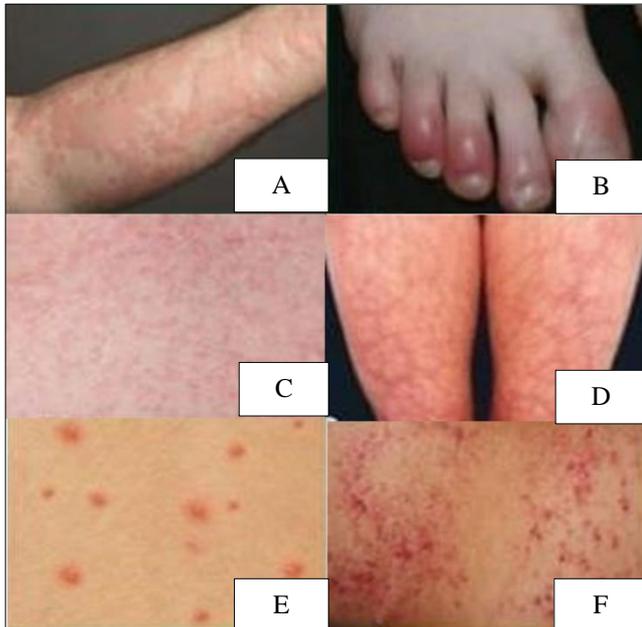


Figure 4: Dermatological manifestations in nCOVID-19 infections; (a) urticaria (b) acral ischemia (c) morbilliform rash (d) livedo reticularis (e) chicken pox like vesicles and (f) petechiae.

Skin manifestations were observed in about one-fifth of a group of patients with COVID-19 in the Alessandro Manzoni Hospital in Lecco, in northern Italy.⁴²

In a study conducted by Recalcati et al, to analyze the cutaneous involvement in nCOVID-19 patients, who were hospitalized in the Lecco Hospital, Lombardy, Italy, 18 patients (20.4%) out of 88, developed cutaneous manifestations. 8 patients developed cutaneous involvement at the onset of disease, 10 patients after the hospitalization. Cutaneous manifestations were erythematous rash (14 patients), widespread urticaria (3 patients) and chickenpox-like vesicles (1 patient). Trunk was the main involved region. Itching was low or absent and usually lesions healed in few days. Apparently, there was no correlation with disease's severity.⁴²

Dr. Jacobs reported a 67-year-old patient who presented with a history of low fever, nasal congestion, postnasal drip, and a wet cough but no shortness of breath. It presented like a common cold. But a week later, the man presented with a non-pruritic blanching livedoid vascular eruption on his right anterior thigh, and also haematuria and weakness. Although vascular eruption and bloody urine resolved in 24 hours, the nCOVID-19 test came back positive and his cough became dry and hacking, and the weakness persisted.⁴²

Another dermatologist also reported a similar transient nCOVID-19 unilateral livedoid eruption.⁴²

It suggests vaso-occlusion. Therefore, nCOVID-19 can feature signs of small blood vessel occlusion which include petechiae or tiny bruises, and transient livedoid eruptions. Whether it's neurogenic, microthrombotic, or immune complex mediated is unknown, but it's a skin finding that can help clinicians as they work up their patients with nCOVID-19 symptoms.⁴² Chen et al pointed out that amongst 48 accumulated nCOVID-19 cases in Thailand, there was an interesting case that presented with a skin rash with petechiae.⁴²

Another important practical concern is the care for patients with autoimmune and chronic inflammatory disorders such as psoriasis, atopic dermatitis, systemic lupus erythematosus, scleroderma, hidradenitis suppurativa which may require immunosuppressive therapy. It is not clear whether immunosuppressive therapy should be delayed.⁴¹ Analyzing these data, we may speculate that skin manifestations are similar to those occurring during common viral infections.

Between a rock and a hard place - the toll on personal protective equipment and personal hygiene on skin

The skin complications in nCOVID-19 are mainly due to hyper-hydration effect of personal protective equipment (PPE), friction, epidermal barrier breakdown, and contact reaction all of which may aggravate an existing skin disease. The most commonly reported skin changes due to PPE are erythema, papules, maceration and scaling. Symptoms include burning, itching and stinging. The most commonly affected skin site include nasal bridge (83% due to the use of protective goggles but not the hygiene mask), cheeks, forehead and hands. A variety of cutaneous diseases ranging from contact and pressure urticaria or contact dermatitis to aggravation of pre-existing dermatides was reported with prolonged contact with goggles and mask. Acne, facial itching and dermatitis from wearing a N-95 mask were reported in more than 1/3rd of health care workers in a study.

Occlusions due to the use of protective hats may induce pruritus and folliculitis or exacerbate seborrheic dermatitis. Long term use of protective gloves leads to occlusion and hyper-hydration state of the epidermis which presents as maceration and erosions, possibly leading to the development of contact dermatitis. Exaggerated hand washing with detergents/ disinfectants can impair the hydro-lipid mantle of the skin surface causing irritation and development of contact dermatitis.

The atopic dermatitis, low humidity, frequency of hand washing, wet work glove use and duration of employment are important risk factors for the development and aggravation of hand dermatitis. Before wearing PPE and following a hand wash, frequent

application of hand cream is advised to prevent contact dermatitis.⁴³

DIAGNOSTIC CRITERIA

The viral research institution in China conducted preliminary identification of the SARS-CoV-2 through the classical Koch's postulates and observing its morphology through electron microscopy.⁴⁴ So far, the golden clinical diagnosis method of nCOVID-19 is nucleic acid detection in the nasal and throat swab sampling or other respiratory tract samplings by real-time PCR and further confirmed by next-generation sequencing.

COMPLICATIONS AND OUTCOME

Complications include acute respiratory distress syndrome (ARDS), arrhythmia, shock, acute kidney injury, acute cardiac injury, liver dysfunction and secondary infection.⁴¹ The poor clinical outcome was related to disease severity. The disease tends to progress faster in elderly people.⁴⁵ Similar to H7N9 patients, the elderly male with comorbidities and ARDS showed a higher death risk.⁴⁶ Neonates and the elderly need more attention and care due to their immature or weak immune system.

TREATMENT

The most effective measure for containment of nCOVID-19 still remains isolation. Therefore, the treatment of nCOVID-19 includes symptomatic care and oxygen therapy. Patients with mild infections require early supportive management. This can be achieved with the use of acetaminophen, external cooling, oxygen therapy, nutritional supplements, and anti-bacterial therapy.¹⁹ Critically ill patients require high flow oxygen, extracorporeal membrane oxygenation (ECMO), glucocorticoid therapy, and convalescent plasma.¹⁹ The administration of systemic corticosteroids is not recommended to treat ARDS.⁴⁶ Moreover, unnecessary administration of antibiotics should also be avoided. Patients with respiratory failure may require intubation, mechanical ventilation, high-flow nasal oxygen, or non-invasive ventilation.⁴⁷ Septic shock requires hemodynamic support with the administration of vasopressors. Therapeutically, aerosol administration of alpha-interferon (5 million units twice daily), chloroquine phosphate, and lopinavir/ritonavir have been suggested.⁴⁸ Other suggested anti-virals include ribavirin and abidor.⁴⁷ The use of three or more anti-viral drugs simultaneously is not recommended. Ongoing clinical studies suggest that Remdesivir (GS5734) can be used for prophylaxis and therapy.⁴⁷

A multi-centric clinical trial regarding the use of mesenchymal stem cell therapy (UCMSCs) for patients with nCOVID-19 is going on globally. Advanced molecular biology and regenerative sciences renders a

breakthrough treatment of severely ill nCOVID-19 patients with mesenchymal stem cells (MSCs). MSCs can help in improving the lung compliance, curb off pneumonia and the agent factor causing the disease per se. The choice of mesenchymal stem cells (umbilical cord or bone marrow or adipose derived) has to be validated.⁴⁸

The therapeutic potential of convalescent sera has been well recognized in major viral outbreaks. Early administration of convalescent plasma or hyper-immune immunoglobulin from patients containing significant antibody titres are likely to reduce the viral load and disease mortality. SARS-CoV-1, H5N1 avian influenza and H1N1 influenza also suggested that transfusion of convalescent plasma was found to be effective and safe.⁴⁹

For PPE induced skin problems use of emollients, barrier creams, moisturizers are essential in preventing skin complications aggravated by preventive measures during pandemic.

Should skin medications maybe continued?

Systemic medications which are used commonly for severe skin conditions include immunomodulators or immunosuppressive drugs, which include a biological agent, a disease modifying anti-rheumatic drug (DMARD), or a systemic steroid.

Dermatological medications are not known to increase the risk of acquiring nCOVID-19.

If you have tested positive for nCOVID-19

- The skin condition is very likely to deteriorate if the systemic medication is stopped suddenly. Therefore, any underlying skin condition or if currently on any medications for the same, the treating doctor must be notified.
- Oral retinoids such as acitretin and isotretinoin can be continued as prescribed.⁵⁰
- If you are taking an immune-suppressive medication, such as cyclosporin, mycophenolate, or azathioprine, or if you are not sure, ask your doctor if you should reduce the dose or stop it.
- If you are taking methotrexate or a biologic agent, the dose should be reduced or the medication must be stopped for at least 4 weeks or until you have fully recovered from nCOVID-19.⁴⁹
- Systemic corticosteroids should not be abruptly discontinued but weaned slowly as advised by your doctor.⁵⁰

If you have cold or flu-like symptoms local guidelines may apply; ask your doctor, if you are on an immunomodulator, a dose reduction or treatment interruption for 2 weeks may be considered, if you are on systemic steroids, ask your doctor if the same dose to be continued, or to reduce the dose or stop it.⁵²

CONCLUSION

Natural disasters bring people together but epidemics and outbreaks split them apart. The SARS-CoV-2 is another CoV that may lead to a pandemic, if not timely controlled. Our current knowledge of this virus suggests an intermediate host; however, human to human transmission is confirmed and is of concern. The skin and nCOVID-19 interaction as well as the consequences to the skin and mucous membranes of increased personal hygiene measures should be recognised by dermatologists and their co-workers.

ACKNOWLEDGEMENTS

We would like to thank Dr. Aishwarya Sivuni, Dermatologist, Celeste Skin, Laser and Hair clinic, Hyderabad, India for literature search regarding nCOVID-19.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: Not required

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Cite this article as: Dheemant M, Sushmitha ES, Jeyaraman M, Ajay SS, Jain R. Unveiling the dermatological manifestations of nCOVID-19. *Int J Res Dermatol* 2020;6:597-603.