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Review Article

Classification and pathophysiology of cutaneous manifestations of COVID-19

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ABSTRACT

Cutaneous manifestation of in COVID-19 patients are varied and needs proper categorization and classification. Various morphological manifestation on skin are seen. The pathophysiology of this virus is not well understood because of it being a novel virus. This disease involves all organs of the body, primarily the respiratory system, heart, kidneys, liver, spleen and the skin as well. In addition to pneumonia which is a hall mark feature of this virus, multiorgan failure occurs as a result of its cascading pathological pathways. Another fatal feature of this virus is hyperimmune response (because of IL-6), known as, 'cytokine storm'. The pathophysiological changes in skin leading to different kinds of rashes range from vasculitis changes to formation of microthrombi obliterating the dermal vessels. After reviewing current literature, we have proposed a simplified classification of cutaneous manifestations of COVID-19 is proposed based on morphological features, relation with severity of disease and histopathological changes. Pathophysiology of cutaneous changes is also being described.

Keywords: Cutaneous manifestations, COVID-19, Classification, Pathophysiology

INTRODUCTION

Coronavirus disease (COVID-19) is caused by SARS-COV2, a potentially fatal disease that is of great global public health concern. Its first case was diagnosed in Wuhan, China on 30 December 2019.[1] The transmission is believed to occur through respiratory droplets, aerosols and contact transmission. The incubation time is generally 3 to 7 days and can be up to 2 weeks as the longest time from infection to symptoms was 12.5 days (95% CI, 9.2 to 18).[2] Patients with COVID-19 show clinical manifestations including fever, dry cough, breathlessness , myalgia, fatigue, normal or decreased leukocyte counts, and radiographic evidence of pneumonia with ground glass appearance on CT chest.[3] Along with the above listed common symptoms, a few dermatological manifestations have also been reported.

For a virus to produce infection, it must gain entry into a susceptible cell within an appropriate host. Viruses usually enter the body via mucous membranes after inhalation, ingestion or contact. The skin can act as a portal of entry, although this usually depends on some breach of the barrier function of the integument. Attachment to the cell surface by means of a receptor is followed by entry of the virion into the cell, by endocytosis or phagocytosis. Viruses differ in the range and type of cell which they can infect; host specificity and tissue tropism are hallmarks of viral infections. After entry into the cell, pre-existing cell enzymes remove or

damage the capsid sufficiently for the nucleic acid to emerge. The next stage depends on the nature of the virus. In relatively simple ones, like enteroviruses, the RNA acts as a messenger, is infectious on its own and is immediately translatable by host ribosomes into viral proteins. More complex RNA viruses, such as influenza, have non-infectious RNA, called negative-strand RNA, which has to be transcribed into messenger RNA (mRNA) by a polymerase enzyme carried in the virus itself. RNA tumor viruses contain a reverse transcriptase enzyme which synthesizes DNA from the viral RNA template. DNA viruses are generally more complex and are able to transcribe mRNA from their DNA using either cell polymerase (e.g. adenoviruses) or viral polymerase (e.g. vaccinia). At the same time, replication of the viral nucleic acid also occurs.[4]

SARS-COV2 virus is a positive strand RNA virus and Spike surface glycoprotein of the virus binds to the host via receptor binding domains of the angiotensin converting enzyme 2 (ACE2), which is most abundant in type II alveolar cells.[5]After a SARS-CoV-2 attaches to a target cell, the virion releases RNA into the cell followed by its replication and thus various manifestations in the host.

METHODS

Literature search was done across PubMed and google scholar using keywords such as COVID-19, cutaneous manifestations in COVID-19, histopathology in skin rashes of COVID-19. 12 articles were chosen including case reports and studies mentioning about cutaneous manifestations in COVID-19. these articles were thoroughly reviewed and a compilation of all cutaneous manifestations with their morphology and histopathology is made.

DISCUSSION

After reviewing current literature on case reports and case studies by clinicians across the world on cutaneous manifestations of COVID-19, various types of rashes in patients of COVID-19 have been reported. Various types of lesions have been described.[6-18] A few classifications of rashes have been explained.[7,8]

A detailed classification of cutaneous manifestations associated with COVID-19 is being proposed on the basis of morphology (Table 1), stage of the disease (Table 2) and histopathology (Table 3).

Morbilliform (maculopapular) rash

It is one of the common rashes in COVID-19. In one study the prevalence of morbilliform rash was found to be 36.1% by Sachdeva et al and 47% in a multicentric study done in Spain by casas et al.[8,7] This rash appears in a comparatively younger age group.[13] It is seen late in the course of disease and is seen in a less severe disease. The lesions appear predominantly on trunk as an erythematous rash.[13] In few instances pin point petechiae have also seen. These lesions are pruritic and or painful. Giannotti described histopathology in a specimen from a hospitalized old patient with papular erythematous exanthema showing oedematous dermis with many eosinophils. Cuffs of lymphocytes around blood vessels in a lymphocytic vasculitis histopathological pattern were observed.[9]

Table 1: Morphological classification.

S. no.	Morphological classification
1.	Morbilliform or maculopapular
2.	Vesicular
3.	Urticarial
4.	Pseudo - chilblain
5.	Necrotic - acral ischaemia, haemorrhagic macules and cutaneous necrosis
6.	Livedo reticularis
7.	Miscellaneous maculopapular - pityriasis rosea like, erythema multiforme, erythema elevatum diutinum, enanthem, flexural rash

Table 2: Classification according to stage/severity of COVID-19.

Stage of disease and cutaneous manifestation	
During asymptomatic stage	Vesicular
During symptomatic stage	
In mild to moderate severity	Pseudo - chilblain
In severe/critical disease	Necrotic - acral ischaemia, haemorrhagic macules and cutaneous necrosis
	Urticarial
	Livedo reticularis

Table 3: Histopathological classification.

Histopathological feature	
Mainly lymphocytic vasculitis	Morbilliform/maculopapular
	Pseudo - chilblains
	Urticarial
	Vesicular
Lesions because of microthrombi/hypercoagulability	Acral ischemia
	Cutaneous necrosis
	Livedo reticularis
	Hemorrhagic macules

Papulovesicular eruption

Papulovesicular lesions have been reported in 34.7%, and 9%, in different studies.[7,8] These lesions are seen more in the middle age group.[7] They appear before the onset of

other symptoms of COVID-19 such as fever, cough, dyspnea etc. and are mostly seen in cases with moderately severe disease. These lesions appear in the form of papules and vesicles appearing all over the body but mainly on trunk and at times on and extremities.[18] These are associated with itching. Recalcati described chicken pox like vesicles in his case series.[6] Casas has reported hemorrhagic vesicles in a few patients.[7] The histology of vesicular lesions has been described to be similar to the rash of Grover disease, showing dyskeratosis, ballooning multi nucleated cells, sparse necrotic keratinocytes with lymphocyte satellitosis. Other findings in these papulovesicular lesions are spongiotic dermatitis with nests of Langerhans cells. Dermal and vessel wall edema, perivascular lymphocytic infiltration and extravasation of RBCs.[9]

Urticarial

Urticarial lesions have been seen more commonly in elderly patients.[7] They appear simultaneously with other symptoms of COVID-19.[7] However, Henry et al described urticarial eruptions in a young patient before the onset of symptoms.[15] These lesions are seen as erythematous weals associated with itching. The prevalence of urticarial lesions is variable in different studies, 9.7% to 19%.[7,8] Urticarial lesions in COVID-19 have been associated with a severe form of the disease with a mortality of 2%.[7] Fernandez et al described histology in urticarial eruption in a COVID-19 patient. Biopsy revealed perivascular infiltrate of lymphocytes, eosinophils and upper dermal edema.[14]

Pseudo chilblains

Pseudo chilblains have been seen with less severe disease and appear late in the disease course.[7] These are mostly seen in younger patients.[16] The lesions are painful and itchy. They appear as patches of erythematous papules and edema.[16] Vesicles and pustules with purpuric areas have also been seen. Chill blains are painful inflammation of small blood vessels in the skin that occur in response to repeated exposure to cold. Due to similar appearance, these lesions have been termed as 'pseudo-chilblains' as there is no association to cold exposure with their appearance. The incidence has been reported to be 19%.[7] Histology of these lesions have shown either vasculitis or thrombi or both. Kolivras et al described violaceous infiltrated plaques in a young COVID-19 patient that appeared abruptly on an erythematous background, with features typical of chilblains.[17] Histopathologic findings simulating chilblain lupus with an absence of significant papillary dermal edema. There was a superficial and deep lymphoplasmacytic infiltrate. Vacuolar interface dermatitis with singly necrotic (apoptotic) keratinocytes and smudging of the basement membrane zone was also seen. The author hypothesized that chilblain lupus erythematosus like lesions in young people should not be confused with the acral ischemia caused by thrombosis that is being observed in severely ill COVID-19 patients as these are possibly due to IFN-1 response and not microthrombi.

Necrotic - acral ischaemia, haemorrhagic macules and cutaneous necrosis

Acral ischemia appears in more severe cases and manifest as gangrenous lesions on toes possibly because of hypercoagulation state in COVID-19 patients.[10] Hemorrhagic rash has also been seen in Covid-19 patients with a more severe disease and high mortality. These appeared as small to big purpuric lesions. Histology of hemorrhagic rash has been described as intravascular microthrombi in the small dermal vessels.[9]

Livedo reticularis

The lesions of livedo reticularis appear as reticulate erythematous rash on trunk, thigs and legs. In some patient's cutaneous necrosis is also reported. They appear in relatively older patients and in more severe disease, associated with higher mortality. Their prevalence is reported to be 2.8-6%.[7,8] Manalo et al from Atlanta proposed that livedo reticularis is caused by conditions, including disseminated intravascular coagulation (DIC), that reduce blood flow through the cutaneous microvasculature system leading to deoxygenated blood accumulation in the venous plexus.[11] Micro thromboses that manifest in other organs (e.g. cardiopulmonary) and as DIC in critically ill COVID-19 patients are the most plausible aetiology to such patients live do reticularis presentations.

Miscellaneous maculo-papular rash

Other lesions like those of pityriasis rosea, erythema multiforme, erythema elevatum diutinum and perifollicular rash with scaling has also been described in 47% of cases associated with itching.[7]

Pathophysiology

COVID-19 being a novel viral disease of hardly 4 months duration has attracted attention of the whole scientific community, but not much has been described about cutaneous manifestations and their pathophysiology. Recalcati was the first to describe cutaneous manifestations in COVID-19.[6] Following which a few cutaneous rashes in COVID-19 were reported from various countries.[6-18]

Tay described that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infects cells expressing the surface receptors angiotensin-converting enzyme 2 (ACE2) and TMPRSS2, the active replication and release of the virus cause the host cell to undergo pyroptosis and release damage-associated molecular patterns, including ATP, nucleic acids and ASC oligomers.[19] This triggers the generation of pro-inflammatory cytokines and chemokines (including IL-6, IP-10, macrophage

inflammatory protein 1α (MIP1α), MIP1β and MCP1). These proteins attract monocytes, macrophages and T cells to the site of infection, promoting further inflammation (with the addition of IFNγ produced by T cells) and establishing a pro-inflammatory feedback loop. In a defective immune response this may lead to further accumulation of immune cells in the lungs, causing overproduction of pro-inflammatory cytokines, which eventually damages the lung infrastructure. The resulting cytokine storm circulates to other organs, leading to multi-organ damage. In addition, non-neutralizing antibodies produced by B cells may enhance SARS-CoV-2 infection through antibody-dependent enhancement (ADE), further exacerbating organ damage. Alternatively, in a healthy immune response, the initial inflammation attracts virus-specific T cells to the site of infection, where they can eliminate the infected cells before the virus spreads. Neutralizing antibodies in these individuals can block viral infection, and alveolar macrophages recognize neutralized viruses and apoptotic cells and clear them by phagocytosis. Altogether, these processes lead to clearance of the virus and minimal lung damage, resulting in recovery.

Different types of exanthems have been seen with different type of viral diseases. This depends upon various factors like host immune reaction and viral load. Any viral exanthem is possibly a delayed type hypersensitivity response, antibody mediated damage, an allergic rash or due to direct damage by virus. Widespread exanthems may be a manifestation of viral infections that cause a viremia. Some microorganisms (e.g. some togaviruses, poxviruses and rickettsiae) can replicate in capillary endothelium, causing damage directly or by a type III hypersensitivity reaction that results in infarcts and hemorrhages. The great majority of viruses, however, act as inert foreign particles, reacting with circulating antibodies and sensitized lymphocytes to produce inflammation. Circulating immune complexes of antibody and viral antigens also localize in dermal blood vessels and are responsible for the rashes in many virus infections, for example human parvovirus. The complex cascade of inflammation in the dermis results in erythematous macules and papules.[20]

COVID-19 exanthem, is also possibly a manifestation of antigen-antibody reaction as antibodies against the virus are formed in infected hosts but these are unable to neutralize the virus and contribute in delayed type of hypersensitivity mediated local damage. Further a direct damage due to the hyperimmune response caused by COVID-19 due to overproduction of early response proinflammatory cytokines (tumour necrosis factor TNF, IL-6, and IL-1β) results in what has been described as a cytokine storm is another possible mechanism causing local damage in the skin. Activation of coagulation pathways during the immune response to infection results in overproduction of proinflammatory cytokines leading to multiorgan injury. Although the main function of thrombin is to promote clot formation by activating platelets and by converting fibrinogen to fibrin, thrombin also exerts multiple cellular effects and can further augment inflammation via proteinase - activated receptors (PARs), principally PAR-1.[21] With reduced anticoagulant concentrations due to reduced production and increasing consumption there is defective procoagulant-anticoagulant balance. This predisposes to the development of micro thrombosis, disseminated intravascular coagulation, and multi - organ failure evidenced in severe COVID-19 pneumonia with raised d-dimer concentrations.[22,23] This mechanism may explain the necrotic, haemorrhagic and livedo reticularis lesions seen in COVID-19 which are a result of occlusion of dermal vessels by microthrombi.

CONCLUSION

COVID-19 disease caused by SARS COV-2 virus most commonly present with fever and upper respiratory tract symptoms such as dry cough and dyspnea. But these symptoms may not be present in all cases. Different types of skin rashes have been seen in COVID-19 patients, appearing at different stages and severity of the disease. Though they might not be a marker of severity of the disease in every case. The cutaneous rashes can also be an inaugural symptom in otherwise asymptomatic cases of COVID-19 which should alert a clinician to rule out the possibility of COVID-19 infection. Cutaneous rashes appearing before onset of typical COVID-19 symptoms are important indicators for suspecting this infection. There are skin rashes like maculopapular/morbilliform, urticarial, pityriasis rosea like rash which appear during the course of milder form of the disease. Whereas other rashes like acral ischemia, necrosis and hemorrhagic rash appear in patients with critical disease thus signifying poor prognosis. Knowledge and understanding of various rashes with their morphological patterns are important and can aid in early detection of COVID-19.

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