VOLUME 10 NOMOR 2 DESEMBER 2023

ISSN 2548 – 611X

JURNAL
BIOTEKNOLOGI & BIOSAINS INDONESIA

Homepage Jurnal: http://ejournal.brin.go.id/JBBI/index

SHORT COMMUNICATION

THE PATHOPHYSIOLOGY OF CUTANEOUS MANIFESTATIONS RELATED TO COVID-19

Patofisiologi Manifestasi Kulit yang Terkait dengan Covid-19

Prasetyadi Mawardi[1,2]*

[1]Department of Dermatology and Venereology, Faculty of Medicine, Sebelas Maret University, Indonesia

[2]Dr. Moewardi General Hospital

*Email: prasetyadi_m@staff.uns.ac.id; prasetyadimawardi@yahoo.com

ABSTRACT

Covid-19 is a respiratory infection caused by the newly emerging coronavirus. Covid-19 can also cause skin abnormalities, although the pathophysiology of manifestations of skin disorders associated with Covid-19 has not been understood with certainty. This study aims to discuss the pathophysiology of cutaneous manifestation related to Covid-19. The study was conducted based on literature and data mining related to Covid-19 using PubMed and Google Scholar. Eligible papers provided pathophysiology of cutaneous manifestations related to Covid-19. Papers not available in English were excluded. As a result of the presence of edema, vasodilation, and cellular infiltration, skin lesions such as rash, urticarial, or extensive purpura, or even thrombosis and haemorrhage, arise if damage to the vessels became severe. The pathophysiology of Covid-19-associated skin manifestations is estimated through some different mechanisms, such as lesions found in various Covid-19 patients, namely, the presence of varicella such as eruption, non-characteristic rash, and urticarial. Further studies are required to establish a Covid-19 diagnosis based on skin manifestations.

Keywords: *Covid-19, pathophysiology, skin abnormalities, skin manifestations*

ABSTRAK

Covid-19 merupakan infeksi saluran nafas yang disebabkan oleh virus corona baru muncul. Virus covid-19 dapat menimbulkan kelainan kulit, meskipun patofisiologi manifestasi kulit yang diakibatkan oleh virus covid-19 belum diketahui secara pasti. Makalah ini bertujuan membahas patofisiologi manifestasi kulit yang disebabkan oleh virus covid-19. Patofisiologi yang menyebabkan ruam pada kulit disebabkan adanya edema, vasodilasi perifer dan infiltrasi seluler, urtikaria, purpura luas atau terjadinya trombosis dan perdarahan, apabila kerusakan pembuluh darah menjadi berat. Mekanisme patofisiologi manifestasi kulit akibat virus covid-19 diperkirakan melalui berbagai mekanisme yang berbeda, seperti erupsi varicella, ruam yang atipik maupun munculnya urtikaria. Penelitian lebih lanjut diperlukan untuk menegakkan diagnosis covid-19 berdasarkan kelainan kulit.

Kata Kunci: Covid-19, patofisiologi, abnormalitas kulit, manifestasi kulit

***Received**: 20 December 2023* ***Accepted**: 30 December 2023* ***Published**: 30 December 2023*

INTRODUCTION

Coronavirus disease of 2019 (Covid-19) is a respiratory infection caused by the newly emerging coronavirus (CoV), which was first encountered in Wuhan, China, around December 2019. Since the World Health Organization (WHO) declared Covid-19 as a global pandemic, more than 200 countries have been infected with this new flu strain (Darlenski and Tsankov 2020). More than five million people were infected with mortality rates above 340,004, as updated on May 23, 2020 at 02:53 GMT, with three countries, namely, the US, the UK**,** and Italy recording the highest mortality rates. Recently, in the end of 2023, Few patients are still infected by SARS-CoV 2 new variant in some countries including Indonesia.

CoVs are classified as single-stranded RNA viruses with positive-sense proteins. With genome sizes ranging from 26 to 32 kilo-bases (kb), CoV has the largest genome for RNA viruses. Based on genetic and antigenic criteria, CoV has been divided into three groups: α-CoVs, β-CoVs, and γ-CoVs. Novel COVID-19 specifically behaves more like SARS-CoV; therefore, it is termed as SARS-CoV 2, which is characterized by the rapid development of acute respiratory distress syndrome followed by multiple organ failure due to cytokine storms in the body, thereby making the morbidity rate of Covid-19 very high (Schoeman and Fielding 2019). Recalcati reported his experience on cutaneous manifestation of Covid-19 patients in Italy (Recalcati 2020). From the medical record-collected data, he deduced that 18 of 88 patients (20.4%) had skin manifestations. Eight patients (9.09%) developed skin manifestations involvement at the onset and ten patients after hospitalization. Cutaneous manifestations were erythematous rash (14 patients, 77.8%), widespread urticaria (3 patients, 21.4%), and varicella-like vesicles (1 patient, 1.8%) (Estébanez et al. 2020). Another skin rash with petechiae has also been described as a possible initial presentation of COVID-19 (Estébanez et al. 2020).

SUBJECTS AND METHODS

The study was conducted electronically to collect the published studies related to Covid-19 using PubMed and Google Scholar. Both review and research paper was included in this study. Eligible papers provided pathophysiology of cutaneous manifestations related to Covid-19. Papers not available in English were excluded.

DISCUSSION

As a result of the presence of edema, vasodilation, and cellular infiltration, skin lesions such as rash, urticarial, or extensive purpura, or even thrombosis and hemorrhage, arise if damage to the vessels became severe. This raises the suspicion that Covid-19 also requires the presence of co-receptors to cause cellular reactions other than that in the main target organ of the respiratory tract and gastrointestinal tract, such as the appearance of symptoms and signs on the skin.

All coronavirus classes have three surface glycoproteins, namely spike (S), envelope (E), and membrane (M). S proteins are a type I membrane glycoprotein that is responsible for the formation of spikes found on the surface of the coronavirus. Furthermore, the S proteins are divided into binding domain receptors, namely, S1 and S2 domain of fusion cell membrane. The SARS-CoV-2 S2 domain represents a higher identity with coronavirus derived from bats than that of the S1 domain (Biswas et al. 2020). The entry of viruses in cells is mediated by spike (S) glycoproteins; in particular, the surface portion of spike 1 (S1) allows binding of the virus to cellular receptors. Later, to allow the entry of viral particles, the S protein is cleaved by cellular proteases at S1 or S2 locations (Hoffmann et al. 2020).

Furthermore, the viral capsid merges with the cellular membrane, which is facilitated by the S2 subunit. It is widely understood that the entrance of SARS-CoV is mediated by angiotensin-converting enzyme 2 (ACE2). The analysis of the order of the receptor-binding motif (RBM) in the receptor-

binding domain reveals that RBM is responsible for binding to ACE2. Further, SARS-CoV and SARS-CoV-2 have stored residues, indicating that their binding to ACE2 could be similar, whereas the same residues do not appear in other coronaviruses. In addition, several antibodies developed against human ACE2 cannot prevent SARS-CoV and SARS-CoV-2 infections (Cava et al. 2020).

The pathophysiology of cutaneous manifestations related to Covid-19 has not been well understood. However, some theories underlie the occurrence of lesions on the skin. In various viral infections, there are three mechanisms for rashes on the skin: the virus first penetrates the skin, with a port d' entre or entrance to the skin, reaches a location where it has the ability to grow, and the lesions are then produced by the virus. If the virus invades and grows on the skin, this may not occur in prodromal lesions or in rashes from certain arbovirus and enterovirus infections. Several aspects of the pathogenesis of skin lesions caused by viruses have been understood, such as Platt's theory (Cava et al. 2020).

The first hypothesis regarding the pathophysiology of cutaneous manifestations related to Covid-19 patients is that for a virus that causes skin lesions with limited growth in the skin, it is easier to distinguish such lesions from lesions that are initiated by viruses that penetrate the skin from the outside compared to by viruses that reach the skin from the inside after spreading throughout the body of infected host, in other words, to distinguish between primary and secondary skin lesions. In several experimental researching, primary lesions produced at the site of virus injection into the skin have been studied. Additionally, some viruses, such as those responsible for warts and papilloma, produce skin lesions only at the site of infection and fail to spread throughout the body. Skin manifestations due to viral infection can be caused by cellular immune response to the skin.[8] Although, many ACE-2 receptors are found in the epidermis, such as keratinocytes in the basal layer or other adnexal glands, cutaneous manifestations associated with Covid-19 do not appear to be through such a mechanism.

The second hypothesis states that secondary skin lesions occur in the course of common viral diseases and will be considered because of localization and growth of the virus in the skin. Viremia can be classified into cell-related viruses and viruses that are free in plasma, although it is sometimes mixed. Important events that are essential for the production of skin lesions are free viruses or infected leukocytes to be localized in small blood vessels in the skin; in many common viral diseases, such as varicella, vascular lesions are the earliest events in the development of skin lesions. To understand the vascular localization of this virus in the skin, we must initially discuss the behavior of inert virus-sized particles when they are inserted into the blood and the evidence for leukocytes passing through the skin's blood vessels (Cava et al. 2020).

The third hypothesis states that viruses growing in the endothelial cells of the blood vessel wall might damage these cells directly, which leads to an inflammatory response. It is known first-hand, through viral antigens contained in endothelial cells in small blood vessels. The reduced catalytic function of ACE-2 could change Renin-Angiotensin-Aldosterone System (RAAS) to increase the response of inflammation and change in vascular permeability. With reference to previous studies, it can be concluded that human fibroblasts have almost the same activity as endothelial cell activity obtained from a pulmonary artery culture (Drago et al. 2017). This can occur in ACE-2, which is also spread in extra pulmonary organs. As a result, there will be an increase in the expression of pro-inflammatory mediators, such as IL-6, IL-8, and various other chemo-attractants that cause vasodilation; endothelial edema; vasculitis; and even angioedema or purpura. In hematolymphoid organ findings, there is no consistent ACE2 expression in immunocompetent cells. The pathological changes in extra-pulmonary organs due to abnormal systemic reactions of cellular immunity are related to viral infections. Abnormalities encountered are systemic vasculitis, apoptosis, or endothelial cell edema (Hamming et al. 2004). Although ACE2 is found in the endothelium cells of all organs, and viruses in the plasma of infected individuals, it does not cause organ

invasion by viruses (Cava et al. 2020; Hamming et al. 2004).

CONCLUSION

The pathophysiology of cutaneous manifestations related to Covid-19 has not been well understood. However, the pathophysiology of Covid-19-associated skin manifestations is estimated through some different mechanisms, such as lesions found in various Covid-19 patients, namely, the presence of varicella such as eruption, non-characteristic rash, and urticarial. Further studies are required to establish a Covid-19 diagnosis based on skin manifestations.

REFERENCES

Biswas A, Bhattacharjee U, Chakrabarti AK, Tewari DN, Banu H, Dutta S (2020) Emer-gence of novel coronavirus and COVID-19: Whether to stay or die out? Crit Rev Micro-biol 46:182-193.

Cava C, Bertoli G, Castiglioni I (2020) In silico discovery of candidate drugs against covid-19. Viruses 12: 404.

Darlenski R, Tsankov N (2020) Covid-19 pandemic and the skin - What should derma-tologists know? Clin Dermatol 38: 785-787.

Drago F, Ciccarese G, Gasparini G, Cogorno L, Javor S, Toniolo A, et al (2017) Con-temporary infectious exanthems: An update. Future Microbiol 12: 171-193.

Estébanez A, Pérez-Santiago L, Silva E, Guillen-Climent S, García-Vázquez A, Ramón MD (2020) Cutaneous manifestations in Covid-19: A new contribution. J Eur Acad Dermatol Venereol 34: e250-e251.

Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H (2004) Tissue distribution of ACE2 protein: The functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol 203: 631-637.

Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al (2020) SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 181: 271-80.e8.

Recalcati S (2020) Cutaneous manifestations in COVID-19: A first perspective. J Eur Acad Dermatol Venereol 3: e212-e213.

Schoeman D, Fielding BC (2019) Coronavirus envelope protein: Current knowledge. Virol J 16: 1-22.