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THE KIDNEY AND SKIN DUO IN SARS-COV-2/COVID-19

Dermatology

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ABSTRACT

SARS-CoV-2 infection has spread to a huge number of countries. After viral exposure, 80% of the cases will behave as mild or asymptomatic, around 15% will require a hospital facility and 5% will require Intensive-Care-Unit (ICU) management and the use of mechanical ventilation. Although SARS-CoV-2 is not as lethal as other severe acute respiratory syndromes (SARS) viruses, it has caused more infections, deaths and economic impact than any other worldwide infectious disease. According to initial pandemic reports, acute kidney injury (AKI) has occurred in around 3-9% of COVID-19 patients, however, not only those numbers have increased up to 20-42% in critically-ill cases and in deceased people, but also, patients with renal involvement seem to have an increased risk of mortality. Similarly, cutaneous manifestations in COVID-19 have presented in around 8-20% of patients and are also subtle at the beginning, but later on they can progress to more severe skin disease. Common COVID-19 pathogenic features seem to be shared by the kidney and the skin and such cutaneous manifestations might be an alert for the need of early kidney function monitoring in order to initiate supportive interventions that may protect such organ from severe renal dysfunction and end stage disease.

KEYWORDS

Skin; Kidney; Sars-CoV-2; COVID-19

INTRODUCTION

By December 12t 2020, SARS-CoV-2 infection has spread to 213 countries, 71.780.957 confirmed cases of infection have been reported, 1.607.304 deaths and 50.308.949 patients recovered. For this same date, of the 19.864.704 actively infected, 19.758.129 (99.5%) are found with mild symptoms and 106.575 (0.5%) in serious or critical condition (source: worldmeters.info). After viral exposure, 80% of the cases will behave as mild or asymptomatic, around 15% will require a hospital facility and 5% will require Intensive-Care-Unit (ICU) management and the use of mechanical ventilation[1]. The need for hospital-based healthcare in those patients with severe or critical illness is responsible for the collapse of the majority of health systems in the world.

Although SARS-CoV-2 is not as lethal as other severe acute respiratory syndromes (SARS) viruses, it has caused more infections, deaths and economic impact than any other worldwide infectious disease. The entry of SARS-CoV coronaviruses into host cells is mediated by a virus-surface spike protein that contains a receptor-binding-domain (RBD) that recognizes the angiotensin-converting enzyme 2 (ACE2) as its receptor[2]. However, an important structural difference in the conformation of the loops in the ACE2-binding ridge between the RBMs of SARS-CoV-2 and SARS-CoV has been recently reported[2]. Other coronavirus receptors involved in viral entry and known to be expressed by endothelial cells include sialic acid receptors , transmembrane serine protease 2 (TMPRSS2) receptor , CD209L and extracellular matrix metalloproteinase inducer (CD147 or basigin), and catepsin B and L[3,4]. These virological features not only define particular virus-host interactions at the molecular level, but also contribute to its efficient transmission and to its wide spectrum of clinical presentations that range from asymptomatic to severe or even fatal cases.

According to initial pandemic reports, acute kidney injury (AKI) has occurred in around 3-9% of COVID-19 patients[5], however, not only those numbers have increased up to 20-42% in critically-ill cases and in deceased people[6,7], but also, patients with renal involvement seem to have an increased risk of mortality[8]. Interestingly, mild renal abnormalities occur at the beginning of Sars-Cov2 infection but could later progress to AKI[9] .Similarly, cutaneous manifestations in COVID-19 have presented in around 8-20% of patients [10,11] and are also subtle at the beginning, but later on they can progress to more severe skin disease. Common potential pathogenic features of kidney and skin manifestations in severe and critically-ill COVID-19 patients are: an excess of expression of the angiotensin II receptor, an elevation of pro-inflammatory cytokines, a vasotropism towards blood-vessels endothelial cells within both organs[12 7]. Such abnormalities contribute to organ/tissue injury, vessel dysfunction and alterations in vascular permeability, a dysregulation of coagulation homeostasis, vasodilation, and endothelial dysfunction with potential development of disseminated intravascular coagulation (DIC) [13-16]. In fact, it seems that viral injured endothelial cells trigger the release of pro-inflammatory mediators and a cascade of events that occur during the coagulation process leading to the production of blood-vessels-microthrombi that in turn cause organ/tissue ischemia[12]. The resultant hypoxemic state not only affects different organs but also contributes to injury in patients with advanced age or with underlying co-morbidities causing a multi organ dysfunction which further increases the mortality risk of those population.

The Kidney in COVID-19

Previous studies have demonstrated that ACE2 is expressed in renal mesangial cells, podocytes, proximal cell brush border, the parietal epithelium of Bowman's capsule, and the collecting ducts [17,18]. COVID-19-related nephropathy seems to occur due to a higher expression of ACE2 that leads to urine abnormalities such as albuminuria, proteinuria, and haematuria in 60-63%, and 26-48% of patients, respectively[7,9]. Haematuria and proteinuria usually present at the first day of hospital admission and can alert physicians for starting renal protective measures[9]. In addition, blood-urea-nitrogen (BUN) seems to start to increase from day 0 to day 16 (Median 2 days)[9], whereas plasma creatinine uric acid(UA) and D-Dimer start to increase at 0 to day 20 (median: 5 days), day 0 to day 20 (median: 7 days) and at day 0 to day 22, respectively[9]. Interestingly, described renal dysfunctions in non-severe COVID-19 patients, have been reported to be mild and are not usually diagnosed as AKI , whereas in severe patients, AKI has been very frequent (66% of severe-ill patients)[9]. In fact, the mortality risk of COVID-19 patients with AKI was reported to be 5.3 times higher than those patients without AKI[9].

Once AKI occurs, it is usually accompanied not only by severe metabolic acidosis in severe Covid-19 infection, but also by mitochondrial dysfunction, acute tubular necrosis, collapsing glomerulopathy, and protein leakage in Bowman's capsule [19,20]. Such

abnormalities are explained not only by an ACE2-dependant pathway, rhabdomyolysis, sepsis, but also an imbalanced renin–angiotensin–aldosterone system, a direct injury of the renal tubules caused by the virus, and the so-called "cytokine storm syndrome", which is characterized by a fulminant and fatal hyper-cytokinemia associated with multi-organ failure. More recently, another author has found signs of kidney infarction what suggests that thrombotic events may also occur in the arterial system and are not limited to the venous system[21]. On the other hand, viral particles found in endothelial cells might cause further endothelial dysfunction, which in turn induces vasoconstriction that causes organ ischaemia, inflammation and a procoagulant state[22]. Although kidney biopsies in COVID-19 could define the localization of the injury, they are difficult to perform not only due to the high risk of exposure of healthcare practitioners but also due to the high risk of bleeding in patients who require anticoagulants and the usual hemodynamic instability found in critically ill patients.

The Skin in COVID-19

A high expression of ACE2/ CD147, TMPRSS2-, and CD26- related genes was found in the skin, however is not yet known if COVID-19-related skin manifestations are explained only by a reaction to the systemic infection or due to viral replication in keratinocytes[23], or both, as viral particles have been reported in the cutaneous blood vessels in patients with COVID-19 infection [24]. Nevertheless, and in line with the presence of a cytokine storm, that affect the lungs, the heart, and the kidney, the spectrum of cutaneous manifestations of COVID-19, seem to be a resultant of an interplay of the humoral and cellular immune response, and possibly due to the formation of reactive oxygen species, the interference of vasodilatory signals, vasculitis of small blood vessels, embolic occlusion of the vessels and/or due to complement activation[25]. In this respect, papulosquamous or perifollicular lesions and viral exanthem like rashes have been suggested to be related with an initial cell mediated response[12]. On the other hand, chicken pox like and zosteriform blisters might be secondary to viremia and a cytopathic effect in keratinocytes[12]. In addition, livedoid and/or pseudo chill-blain lesions seem to be the resultant of small to medium vessel occlusion either due to hypoxia, microthrombi formation or immune complex deposition [13,26,27](Figures 1, 2A, 2B). In fact, pernio-like lesions have been reported to appear either concurrently with or after COVID-19 symptoms[28], and interestingly, in a very large worldwide registry, 174 out of 318 patients with suspected or confirmed COVID-19 more than half of the population (55%), presented only with pernio-like cutaneous lesions[28]. In addition, and according to the results of a prospective nationwide consensus study in Spain that included 375 cases[29], five COVID-19 clinical cutaneous patterns have been seen: 1) Maculopapular eruptions in 47% patients); 2) Acral areas of erythema with vesicles or pustules (pseudo-chilblains) in 19% patients; 3) Urticarial lesions (19%); 4) Vesicular eruptions (9%); 5) Livedoid or necrotic lesions (6%)[29]. Interestingly, maculopapular and vesicular eruptions seem to appear early in the course of the disease and chilblain-like lesions frequently appear late whereas the other patterns tend to develop in between the aforementioned skin manifestations.

Given these findings, skin manifestations in the COVID-19 pandemic can be an early sign of viral infection and could assist clinicians either to suspect or recognize the disease which could be particularly useful in asymptomatic patients. Also, as renal and skin lesions share some pathogenic and vessel dysfunction features, skin manifestations could alert for the need of early kidney function monitoring regardless of the presence of chronic comorbidities. In turn, supportive interventions at the early stage of COVID-19 illness could potentially protect the kidney from severe renal dysfunction and end stage disease.

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Conflicts Of Interests:

The authors have no conflict of interest to declare

Figure Legends:

Figure 1: Low power view highlighting dermal oedema, minimal perivascular inflammation and dilated thrombosed small blood vessels.

Figures 2 A & B. Higher magnification showing the thrombi (A) and highlighted by PAS (B)

REFERENCES

1 Wang Y, Chen Y, Qin Q. Unique epidemiological and clinical features of the emerging 2019 novel coronavirus pneumonia (COVID-19) implicate special control measures. J Med Virol. 2020; 92: 568-76.
2 Shang J, Ye G, Shi K et al. Structural basis of receptor recognition by SARS-CoV-2. Nature. 2020; 581: 221-4.
3 Sardu C, Gambardella J, Morelli MB et al. Hypertension, Thrombosis, Kidney Failure, and Diabetes: Is COVID-19 an Endothelial Disease? A Comprehensive Evaluation of Clinical and Basic Evidence. J Clin Med. 2020; 9.
4 Ou X, Liu Y, Lei X et al. Characterization of spike glycoprotein of SARS-CoV-2 on virus entry and its immune cross-reactivity with SARS-CoV. Nat Commun. 2020; 11: 1620.
5 Durvasula R, Wellington T, McNamara E et al. COVID-19 and Kidney Failure in the Acute Care Setting: Our Experience From Seattle. Am J Kidney Dis. 2020.
6 Fanelli V, Fiorentino M, Cantaluppi V et al. Acute kidney injury in SARS-CoV-2 infected patients. Crit Care. 2020; 24: 155.
7 Gabarre P, Dumas G, Dupont T et al. Acute kidney injury in critically ill patients with COVID-19. Intensive Care Med. 2020.
8 Pei G, Zhang Z, Peng J et al. Renal Involvement and Early Prognosis in Patients with COVID-19 Pneumonia. J Am Soc Nephrol. 2020; 31: 1157-65.
9 Li Z, Wu M, Guo J et al. Caution on kidney dysfunctions of 2019-nCoV patients. medRxiv 2020.02.08.20021212; doi: https://doi.org/10.1101/2020.02.08.20021212.
10 Recalcati S. Cutaneous manifestations in COVID-19: a first perspective. J Eur Acad Dermatol Venereol. 2020; 34: e212-e3.
11 De Giorgi V, Recalcati S, Jia Z, Chong W, Ding R, Deng Y, Scarfi F, Venturi F, Trane L, Gori A, Silvestri F, Gao XH, Lotti T. Cutaneous manifestations related to coronavirus disease 2019 (COVID-19): A prospective study from China and Italy. J Am Acad Dermatol. 2020 Aug;83(2):674-675. doi: 10.1016/j.jaad.2020.05.073.
12 Garg S, Garg M, Prabhakar N et al. Unraveling the mystery of Covid-19 Cytokine storm: From skin to organ systems. Dermatol Ther. 2020: e13859.
13 Huang C, Wang Y, Li X et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020; 395: 497-506.
14 Helms J, Tacquard C, Severac F et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. Intensive Care Med. 2020; 46: 1089-98.
15 Goshua G, Pine AB, Meizlish ML et al. Endotheliopathy in COVID-19-associated coagulopathy: evidence from a single-centre, cross-sectional study. Lancet Haematol. 2020.
16 Huertas A, Montani D, Savale L et al. Endothelial cell dysfunction: a major player in SARS-CoV-2 infection (COVID-19)? Eur Respir J. 2020.
17 Hamming I, Timens W, Bulthuis ML et al. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol. 2004; 203: 631-7.
18 Martinez-Rojas MA, Vega-Vega O, Bobadilla NA. Is the kidney a target of SARS-CoV-2? Am J Physiol Renal Physiol. 2020; 318: F1454-F62.
19 Su H, Yang M, Wan C et al. Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. Kidney Int. 2020; 98: 219-27.
20 Ronco C, Reis T, Husain-Syed F. Management of acute kidney injury in patients with COVID-19. Lancet Respir Med. 2020.
21 Post A, den Deurwaarder ESG, Bakker SJL et al. Kidney Infarction in Patients With COVID-19. Am J Kidney Dis. 2020.
22 Varga Z, Flammer AJ, Steiger P et al. Endothelial cell infection and endotheliitis in COVID-19. Lancet. 2020; 395: 1417-8.
23 Radzikowska U, Ding M, Tan G et al. Distribution of ACE2, CD147, CD26 and other SARS-CoV-2 associated molecules in tissues and immune cells in health and in asthma, COPD, obesity, hypertension, and COVID-19 risk factors. Allergy. 2020.
24 Criado PR, Abdalla BMZ, de Assis IC, van Blarcum de Graaff Mello C, Caputo GC, Vieira IC. Are the cutaneous manifestations during or due to SARS-CoV-2 infection/COVID-19 frequent or not? Revision of possible pathophysiologic mechanisms. Inflamm Res. 2020 Aug;69(8):745-756. doi: 10.1007/s00011-020-01370-w.
25 Magro C, Mulvey JJ, Berlin D 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.
26 Marzano AV, Genovese G, Fabbrocini G et al. Varicella-like exanthem as a specific COVID-19-associated skin manifestation: Multicenter case series of 22 patients. J Am Acad Dermatol. 2020; 83: 280-5.
27 Gianotti R, Veraldi S, Recalcati S et al. Cutaneous Clinico-Pathological Findings in three COVID-19-Positive Patients Observed in the Metropolitan Area of Milan, Italy. Acta Derm Venereol. 2020; 100: adv00124.
28 Freeman EE, McMahon DE, Lipoff JB, Rosenbach M, Kovarik C, Takeshita J, French LE, Thiers BH, Hruza GJ, Fox LP; American Academy of Dermatology Ad Hoc Task Force on COVID-19. Pernio-like skin lesions associated with COVID-19: A case series of 318 patients from 8 countries. J Am Acad Dermatol. 2020 Aug;83(2):486-492. doi: 10.1016/j.jaad.2020.05.109.
29 Galván Casas C, Català A, Carretero Hernández G, Rodríguez-Jiménez P, Fernández-Nieto D, Rodríguez-Villa Lario A, Navarro Fernández I, Ruiz-Villaverde R, Falkenhain-López D, Llamas Velasco M, García-Gavín J, Baniandrés O, González-Cruz C, Morillas-Lahuerta V, Cubiró X, Figueras Nart I, Selda-Enriquez G, Romaní J, Fustà-Novell X, Melian-Olivera A, Roncero Riesco M, Burgos-Blasco P, Sola Ortigosa J, Feito Rodriguez M, García-Doval I. Classification of the cutaneous manifestations of COVID-19: a rapid prospective nationwide consensus study in Spain with 375 cases. Br J Dermatol. 2020 Jul;183(1):71-77. doi: 10.1111/bjd.19163.
30 Diao B, Wang C, Wang R et al. Human Kidney is a Target for Novel Severe Acute. Respiratory Syndrome Coronavirus 2 (SARS-Cov-2) infection In: medRxiv 2020.03.04.20031120; doi: https://doi.org/10.1101/2020.03.04.20031120.