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Cutaneous manifestations associated with anosmia, ageusia and enteritis in SARS-CoV-2 infection – A possible pattern? Observational study and review of the literature



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ABSTRACT

Background: The cutaneous manifestations of coronavirus disease 2019 (COVID-19) have been covered insufficiently in the literature.

Methods: Thirty-nine patients admitted to the study hospital with confirmed COVID-19 who experienced various skin manifestations during hospitalization or in the convalescence period, were analysed retrospectively.

Results: Thirty-nine patients with COVID-19, admitted to the study hospital between 23 March and 12 September 2020, had intra-infectious rash or lesions of cutaneous vasculitis during convalescence. The most common cutaneous manifestations of COVID-19 were erythematous and erythematous papular rash. Twenty-seven of the 39 patients had anosmia (69.2%), 26 patients had ageusia (66.7%), 34 patients had pneumonia (87.2%) and 24 patients had intra-infectious enterocolitis (61.5%). Skin biopsies were rarely performed in these patients. This article reports the results of biopsies performed in two patients, showing histopathological and immunohistochemical changes in erythematous rash and erythema multiforme-like lesions. Both skin biopsies revealed early fibrous remodelling of the dermis, suggesting similarity with changes that occur in the lungs and other tissues in patients with COVID-19.

Conclusions: Correlations between skin lesions and anosmia, ageusia and enteritis in patients with COVID-19 do not seem to be accidental, but are associated with a similar response to ACE2 receptor expression in these tissues.

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Background

The expression levels of ACE2 receptors in various human tissues may be responsible for the pathogenesis of coronavirus disease 2019 (COVID-19). The presence of ACE2 receptors in the respiratory system, cardiovascular system, digestive tract (oesophageal mucosa, ileum), kidneys and uroepithelium explains their involvement in the context of COVID-19. Skin involvement in patients with COVID-19 has not received much research attention,

either clinically or histopathologically. The Academic Emergency Hospital, Sibiu, Romania was involved from the beginning in the treatment of patients with COVID-19.

This study aimed to evaluate the dermatological aspects and changes found in 39 patients with COVID-19, and the histopathological and immunohistochemical changes in two cases with erythematous rash and erythema multiforme-like lesions.

In the initial phase, skin lesions are produced by direct action of the virus on the epidermis. Direct vascular lesions can be a cause for epidermal manifestations through haematogenous dissemination (lymphocytic thrombophilic arteritis) (Lee et al., 2008). Immunological mechanisms can also be a contributory factor due to an excess of proinflammatory cytokines or autoimmune mechanisms, as suggested previously (Diotallevi et al., 2020). In

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vascular lesions, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) stimulates CD4+ T lymphocytes to produce proinflammatory cytokines (IL-1, IFN- γ , and TNF- α), and recruits eosinophils, CD8+ T lymphocytes, B cells and natural killer (NK) cells which target keratinocytes. Expression of ACE2 receptors in the epidermis and digestive cells, cerebral tissues and vascular tissues is positively correlated with the level of CD8+ T lymphocytes, interferon, B cells and NK cells in both females and males (Li et al., 2020).

Materials and methods

A single-centre observational cohort study on patients with COVID-19 is underway at the Academic Emergency Hospital, Sibiu, Romania, a county hospital with 1054 beds dedicated to the treatment of patients with COVID-19. This study undertook a retrospective analysis of 39 patients admitted to the study hospital with confirmed COVID-19 [by real-time reverse transcriptase-polymerase chain reaction (RT-PCR) from nasal and pharyngeal swabs] who experienced various skin manifestations during hospitalization or in the convalescence period. Detailed information regarding the enrolled cases was abstracted from the medical records of patients. All data were available for all enrolled patients. Written informed consent was obtained from the patients for publication of their case reports and any accompanying images. This study was approved by the hospital ethics committee.

Results

Between 23 March and 12 September 2020, 39 patients with COVID-19 with an intra-infectious rash or lesions of cutaneous vasculitis during convalescence were admitted to the study hospital, representing 3.91% of 997 patients with COVID-19 hospitalized in the Infectious Diseases Clinic. Twenty-one of 39 patients were female (53.8%) and 18 patients were male.

Twenty-seven of 39 patients had anosmia (69.2%), 26 patients had ageusia (66.7%), 34 patients had pneumonia (87.2%) and 24 patients had intra-infectious enterocolitis (61.5%), suggesting correlation between ectoderm-derived cells and the affinity of SARS-CoV-2 for this type of cell. In four cases, the rash was preceded by fever; the rash was generalized in all four cases. Two of the cases showed a scarlet-fever-like eruption with subsequent furfureaceous desquamation. One case experienced syncope during the course of disease.

Only two cases of skin lesions occurred after the patients were discharged from hospital; these lesions had a vasculitis appearance. The remaining cases occurred between 2 and 25 days of hospitalization. In 36 cases, SARS-CoV-2 had been identified at the time of the rash, suggesting its direct action on the epidermis.

Skin lesions identified in the study patients were: maculopapular eruptions (12 cases); disseminated erythematous rash (12 cases); localized erythematous rash, mainly on trunk (four cases); scarlet-fever-like lesions (two cases); petechial rash (two cases); erythema multiforme-like lesions (two cases); urticarial lesions (two cases), chilblain-like lesions or 'COVID toes' (one case); erythematous papulovesicular lesions (one case); and upper limb necrotic lesions in the context of consumptive coagulopathy (one case).

Three of the critical patients with SARS-CoV-2 pneumonia and respiratory distress presented erythema multiforme-like lesions, maculopapular eruptions and/or necrotic lesions in the context of disseminated intravascular coagulation. The most important aspects are shown in Figures 1–7.

Discussion

Recalcati (2020) described correlation of skin lesions with COVID-19, with 18 of 88 (20.4%) patients with COVID-19 presenting



Figure 1. Erythematous rash (pink-red round macules, merged in extensive placards, with a tendency to generalize).



Figure 2. Erythematous papular rash with annular pattern (erythematous papules with annular aspect, round or oval shape, well delimited, tendency of confluence in plates and placards at the level of the upper limbs and the cephalic extremities).

with skin lesions. Eight patients had skin manifestations during hospitalization and 10 patients after discharge. Fourteen patients had skin rashes, three patients had urticaria and one patient had vesicular manifestations. In the present study, a rash appeared immediately after hospital discharge in two cases; patients were discharged when viral clearance was achieved (repeated negative RT-PCR swab test for SARS-CoV-2 at 24 h) (Iancu et al., 2020). The second case presented with left hallux chilblain-like lesions or 'COVID toes'. The remaining cases were diagnosed during hospitalization in parallel with the persistence of SARS-CoV-2 on nasal and pharyngeal control swabs.

In February 2020 in China, Guan et al. (2020) reported two cases of skin rash among 1099 patients with COVID-19 (0.2%).



Figure 3. Erythematous papulovesicular rash (multiple erythematous papulovesicular lesions, prurigo-like, round shape, associated with pruritus, localized on the anterior thorax, secondary erosions due to scratching).



Figure 4. Purpuric rash (persistent, disseminated, discreetly contoured, localized on the anterior neck and thorax, erythematous-petechial lesions).



Figure 5. Vasculitis lesions (painful erythematous papules lesions with purpuric aspect, round, convergent into acral plates or isolated on the foot and ankle).



Figure 6. Chilblain-like lesions (persistent and discreetly contoured purplish lesions with acral distribution).



Figure 7. Acro-ischaemia in a patient with coronavirus disease 2019 in the context of disseminated intravascular coagulation (intense acral cyanosis of fingers 1 and 2 of the right hand).

In the present study, 3.91% of patients with COVID-19 had cutaneous manifestations, and the most common were erythematous rash and maculopapular eruptions.

A French observational study by [Bouaziz et al. \(2020\)](#) captured several aspects of skin lesions: rash; chicken-pox-like vesicles; cold urticaria; petechial rash; livedo, necrotic and non-necrotic purpura; chilblain-like lesions with or without Raynaud's phenomena; and cherry angioma. [Annunziata et al. \(2020\)](#) reported four cases of erythematous papular rash and urticarial lesions with onset 3–9 days after the onset of COVID-19 respiratory manifestations. [Manalo et al. \(2020\)](#) described two cases of livedo reticularis as cutaneous manifestations associated with COVID-19, secondary to dermal vascular microthrombosis, and [Jimenez-Cauhe et al. \(2020\)](#) described a case of petechial rash.

[Zhang et al. \(2020a\)](#) described acro-ischaemic lesions in seven patients, as well as lesions in the context of disseminated intravascular coagulation in four critical patients. Moreover, skin lesions were present in three patients with coagulopathy and antiphospholipid antibodies ([Zhang et al., 2020b](#)); similar lesions on the limbs are shown in [Figure 7](#) from the first patient diagnosed at the study hospital. The patient had respiratory distress, multiple organ failure and disseminated intravascular coagulation. Dosing of antiphospholipid antibodies was not performed in order to potentially support the double cause of lesions, labelled in the context of disseminated intravascular coagulation and antiphospholipid syndrome.

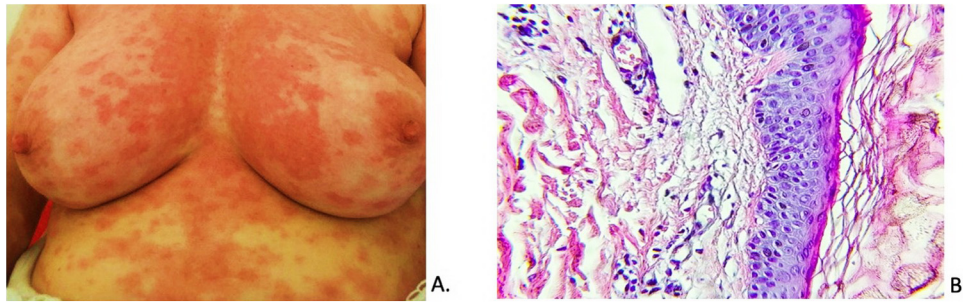


Figure 8. (A) Erythema multiforme-like lesions (a target erythematous papules lesions, disseminated, well contoured, with a tendency of confluence in placards at the thoraco-abdominal level). (B) Microscopic aspect of skin biopsy (keratinized stratified squamous epithelium with a tendency for atrophy with diffusively erased contours of the epidermal ridges, dermal oedema and perivascular lymphocytic infiltrate) (haematoxylin and eosin, original magnification 400×).

Dertlioğlu (2020) reported five cases of rash with the same pattern as noted by the present authors, anosmia and ageusia in the presence of SARS-CoV-2 virus in nasopharyngeal swabs, with the appearance of annular erythema, erythematous or erythematous papular rash with spontaneous remission. The rash occurred in young people without comorbidities. Also, in the present study, viral rash associated with anosmia and ageusia occurred in patients with mild-to-moderate disease who did not require respiratory support.

Skin biopsies were rarely performed in these patients. The histological dynamics were present in the evolution of the rash, as

well as various aspects of the lesions that may be associated with COVID-19.

Gianotti et al. (2020) described the histological changes in two patients with COVID-19. The first case had an erythematous rash located at the level of the thorax; Gianotti et al. highlighted the presence of dyskeratosis cells, associated with ballooned multinucleated cells, necrotic keratinocytes and satellite lymphocyte infiltrate. The second case had diffuse lymphocytic vasculitis with microthrombi.

In the present study, skin biopsies were performed in two cases. The first case [erythema multiforme-like rash (Figure 8A) had a

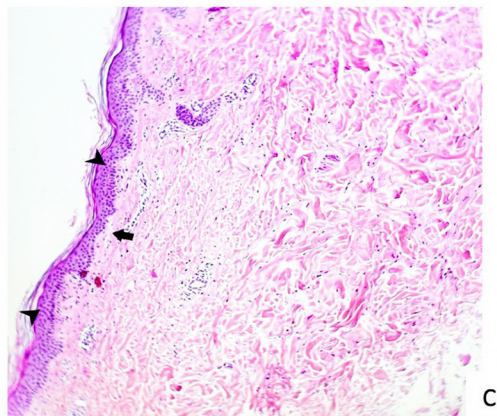
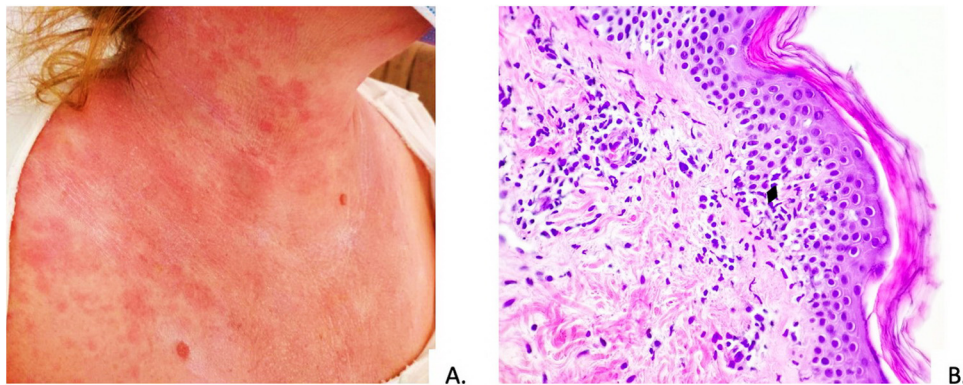


Figure 9. (A) Erythematous rash. (B) Histopathological aspect of skin biopsy [focal area of spongiosis with lymphocytic exocytosis (diamond)] (haematoxylin and eosin, original magnification 400×). (C) Microscopic aspect of skin biopsy [keratinized stratified squamous epithelium with a tendency for atrophy with diffusively erased contours of the epidermal ridges (arrowhead) and fibrosis of the superficial dermis (arrow)] (haematoxylin and eosin, original magnification 100×).

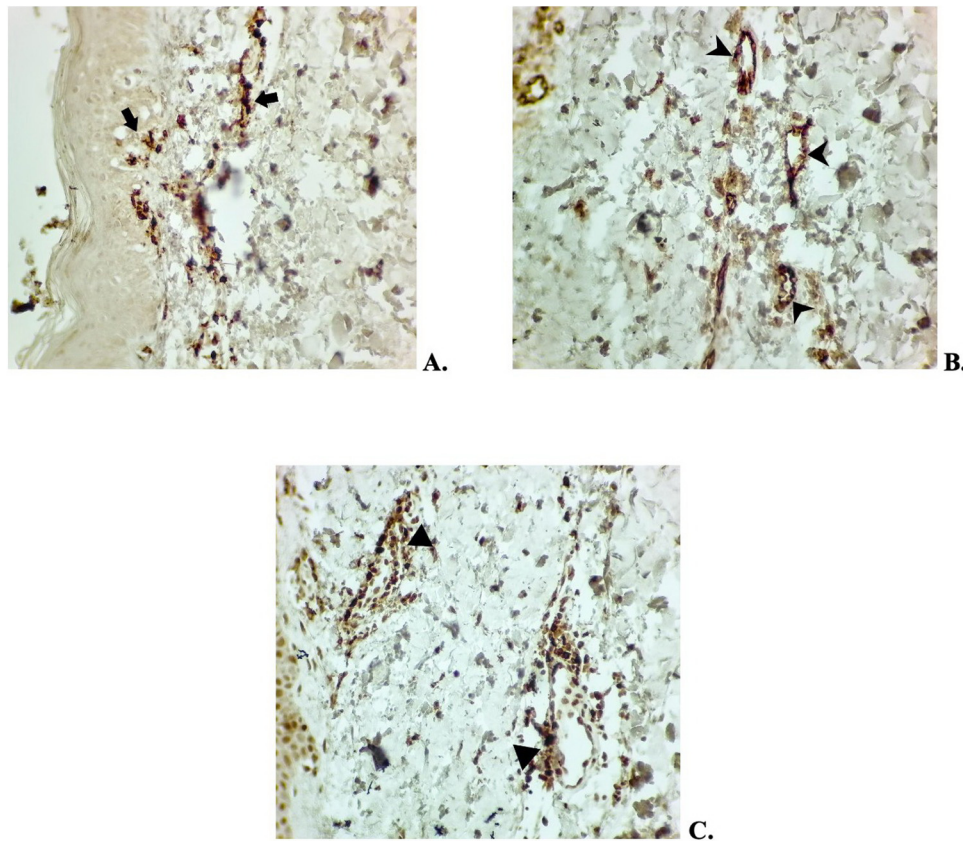


Figure 10. Immunohistochemical study of skin biopsy. (A) (arrows) CD3-positive T lymphocytes in the perivascular region and the epidermis [immunohistochemistry (IHC), original magnification 400 \times]. (B) (arrow heads) CD31-positive endothelial layer (IHC, original magnification 400 \times). (C) (triangles) CD45-positive lymphocytes which tend to invade the blood vessel walls (IHC, original magnification 400 \times).

dermo-epidermal inflammatory lesion without criteria for a specific histopathological category. Microscopic examination of this biopsy, using haematoxylin and eosin stain, revealed a stratified keratinized squamous epithelium with a tendency for atrophy with diffusively erased contours of the epidermal ridges, minimal hyperkeratosis and preserved delimitation of the epidermal layers. The granular layer was present throughout. The spinous layer had a basaloid pattern in the inferior third secondary to a reactive process. The basal layer had no histological modifications, and the dermo-epidermal junction was intact. The superficial dermis sustained fibrous remodelling containing thick horizontal collagen fibres. Blood vessels from the superficial and deep dermis had intact walls, endothelium of normal histological appearance with slight perivascular oedema, and moderate perivascular lympho-monocyte inflammatory infiltrate. In some areas, the inflammatory infiltrate outlined invasion of the vascular wall, but without the presence of fibrinoid necrosis on the examined material (Figure 8B).

Microscopic examination of the second skin biopsy (Figure 9A) revealed similar histopathological changes as the first biopsy but at a higher level. The keratinized stratified squamous epithelium had a tendency for atrophy with diffusively erased contours of the epidermal ridges and moderate hyperkeratosis. Small focal areas of spongiosis were present within the spinous layer, with some squamous cells that had a large round hyperchromatic nucleus, with a perinuclear halo but no cytoplasmic or nuclear inclusions. Areas of vacuolization were found within the basal layer with focal areas of destruction of the dermo-epidermal junction by lymphocytic exocytosis, with small lymphocytes invading the epidermis up to the superior third of the spinous layer. As in the first case, the superficial dermis suffered fibrous remodelling. The small blood

vessels of the papillary and reticular dermis had preserved endothelium, marked perivascular oedema and rich perivascular lymphocyte-predominant inflammatory infiltrate with a tendency to invade the vascular wall, but with no presence of fibrinoid necrosis or erythrocyte extravasation on the examined material (Figure 9B,C).

Both skin biopsies revealed early fibrous remodelling of the dermis, suggesting similarity with changes that occur in the lungs and other tissues in patients with COVID-19.

An extended panel of antibodies – CD3, CD5, CD10, CD20, CD23, CD30, CD31, CD45 and CD79 – was used for immunohistochemical analysis of the two skin biopsies. It was concluded that almost all of the inflammatory infiltrate in the perivascular region as well as in the epidermis was composed of CD3-positive T lymphocytes. No B lymphocytes were found on the tissue specimens examined. CD31 staining showed a preserved endothelial layer on the blood vessels, although CD45 staining showed that the inflammatory infiltrate was concentrated very close to blood vessels, and tended to invade blood vessel walls (Figure 10).

Fernandez-Nieto et al. (2020) presented a case of urticarial rash which occurred on the 6th day of hospitalization. Histological examination revealed lymphocytic perivascular infiltrate, eosinophils and dermal oedema.

In the digestive tract, more ACE2 expression occurs in the ileal epithelium (approximately 30% of cells are positive for ACE2 receptors) compared with the oesophagus (1%), stomach and liver (<1%) (Zou et al., 2020), explaining the presence of diarrhoeal stools as the most common digestive manifestation in COVID-19. In the authors' experience, rash during hospitalization was most often associated with a digestive episode, suggesting viraemia during which SARS-CoV-2 binds to ACE2 receptors in various

tissues, as well as possible correlation with CD8+ T lymphocytes, interferon, B cells and NK cells. Occasionally, patients reported a dry mouth or a persistent bitter taste at the onset of disease or as disease progressed.

Other authors have reported the presence of diarrhoea with SARS-CoV-2 invasion in the digestive tract, especially in enterocytes (Donoghue et al., 2000; Crackower et al., 2002; Harmer et al., 2002; Hamming et al., 2004; Kowalczyk et al., 2008) associated with the presence of viraemia.

The main limitations of this study were the small number of enrolled patients (39 patients with cutaneous manifestations), and the small number of histopathological examinations performed.

Conclusions

Correlations between skin lesions and anosmia, ageusia and enteritis in patients with COVID-19 do not seem to be accidental, but are associated with a similar response to ACE2 receptor expression in these tissues, in direct correlation with the immune response of CD8+ T lymphocytes cells, B cells and NK cells. Both skin biopsies revealed early fibrous remodelling of the dermis, suggesting similarity with changes that occur in the lungs and other tissues in patients with COVID-19. Further observational studies are needed to support this finding.

Conflict of interests

None declared.

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Ethical approval

This study was approved by the hospital ethics committee. Written informed consent was obtained from the patients for publication of their case reports and any accompanying images.

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