



Clinicopathological Features of Cutaneous Findings of SARS-CoV-2 Infection

SARS-CoV-2 Pozitif Hastaların Kutanöz Bulgularının Klinik-patolojik Özellikleri

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ABSTRACT

Objective: In December 2019, severe acute respiratory syndrome coronavirus-2, which emerged in Wuhan, China, spread rapidly and created a pandemic. Coronavirus disease-2019 (COVID-19) can affect different organ systems, including the skin. Recently, COVID-19 cases with skin lesions of different clinicopathological features have been published. This study aimed to present the histopathological features of 19 COVID-19 cases with cutaneous findings and discuss them in light of the literature.

Methods: Skin biopsy specimens of 19 patients with skin rashes associated with COVID-19 were evaluated histopathologically and clinically.

Results: Clinical manifestations of rashes developed in eight female, seven male, and four pediatric patients with COVID-19. Urticaria/urticarial vasculitis (n=7), maculopapular eruption (n=7), panniculitis (n=2), purpuric eruptions (n=2), and livedoid-like lesions were noted. Histopathologically, besides the inflammatory findings, the most striking feature was that the vessels were more or less affected in almost all cases.

Conclusions: Cutaneous lesions associated with COVID-19 are increasingly being reported. We believe that every data presented about this disease, which has many unknowns, will shed light on future research. Every case can lead us a new way.

Keywords: SARS-CoV-2, skin, pathology

ÖZ

Amaç: Aralık 2019'da Çin'in Wuhan kentinde ortaya çıkan ve şiddetli akut solunum sendromu koronavirüs-2 olarak adlandırılan patojen hızla yayılarak pandemiye yol açmıştır. Bilindiği gibi koronavirüs hastalığı-2019 (COVID-19), deri de dahil olmak üzere farklı organ sistemlerini etkileyebilir. Son zamanlarda, farklı klinikopatolojik özelliklere sahip deri lezyonları olan COVID-19 olguları yayınlanmıştır. Burada sunulan makalenin amacı deri bulguları olan 19 COVID-19 pozitif olgunun histopatolojik özelliklerini sunmak ve literatür ışığında tartışmaktır.

Yöntemler: COVID-19 enfeksiyonu sırasında deri döküntüsü olan 19 hastanın deri biyopsisi örnekleri histopatolojik ve klinik olarak değerlendirildi.

Bulgular: COVID-19 ile enfekte sekiz kadın, yedi erkek ve dört çocuk hastada gelişen döküntülerin klinik belirtileri; ürtiker/ürtikeryal vaskülit (n=7), makülopapüler döküntü (n=7), pannikülit (n=2), purpurik döküntü (n=2) liveoid benzeri paterndeydi. Histopatolojik olarak enflamatuvar bulguların yanı sıra en çarpıcı özellik, hemen bütün olgularda damarların az ya da çok etkilenmiş olmasıydı.

Sonuçlar: COVID-19 ile ilişkili deri lezyonları giderek daha fazla rapor edilmektedir. Pek çok bilinmeyen olan bu hastalık hakkında sunulan her bilginin ileride yapılacak araştırmalara ışık tutacağına inanıyoruz. Her olgu bize yeni bir yol gösterebilir.

Anahtar kelimeler: SARS-CoV-2, deri, patoloji

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INTRODUCTION

Since the end of 2019, the infection caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) continues to spread rapidly worldwide. According to the Worldometers website where coronavirus disease-2019 (COVID-19) data were compiled, the total number of cases detected in Wuhan city, Hubei province, China, and worldwide exceeded 379 million (June 2021)^{1,2}.

SARS-CoV-2 is an enveloped virus composed of positive-sense single-stranded RNA and belongs to the coronavirus family. The virus is transmitted by inhalation of droplets through coughing and sneezing. The virus attaches to the respiratory epithelium using angiotensin-converting enzyme 2 (ACE-2). After an average incubation period of 5-6 days (4-14), the disease usually begins with fever, cough, and fatigue. The disease may show different symptoms depending on the individual^{3,4}.

Once the virus is ingested through the respiratory system, it affects many organs. To date, many COVID-19 cases presenting cutaneous findings have been reported^{2,4-11}.

As information about COVID-19 increases, more skin biopsies are being taken. We examined the histological features of skin biopsies of 19 patients with COVID-19 and cutaneous involvement.

MATERIALS and METHODS

In this study, after ethics committee approval from the Istanbul Medeniyet University of Goztepe Training and Research (decision no: 2022/0233, date: 13.04.2022), the histopathological features of skin biopsies of 19 patients

with SARS-CoV-2-positive nasopharyngeal swabs and accompanying cutaneous findings since March 2020 were evaluated. Skin biopsies were obtained under local anesthesia after taking informed consent from the patient. After routine follow-up procedures in pathology, they were stained with hematoxylin-eosin and examined under light microscopy (CX43, Olympus, Japan). Biopsies were also obtained for direct immunofluorescence examination from three patients suspected of vascular lesions and stained with immunoglobulin (Ig) G, Ig A, Ig M, Ig D, and fibrinogen (Polyclonal Rabbit antihuman, FITC, Dako, Denmark) and examined under a fluorescent microscope (BX-53, Olympus). Images were taken using Olympus DP-72. Only skin biopsies of patients with COVID-19 and rash were analyzed.

Statistical Analysis

Statistical analyses were not performed because of the small number of patients.

RESULTS

This study analyzed histopathological findings of the skin biopsy samples taken from 19 patients who were hospitalized for skin lesions and COVID-19. Of the 19 patients, 8 were female, 7 were male, and 4 were pediatric patients (3 girls and 1 boy). The age range of the patients was broad (mean age, 41.4; range, 5-82 years). All adult patients had symptoms of active disease. One of the girls had mild signs, and two were asymptomatic. The boy was diagnosed with multisystem inflammatory syndrome in children (MIS-C). Clinical and histopathologic findings are shown in Table 1. Clinical manifestations included urticaria/

Table 1. Clinical and histopathologic findings.

Clinical manifestation	Histopathologic findings
Urticaria/urticarial vasculitis (n=7)	Dermal edema, perivascular lymphocyte, and eosinophil infiltration (n=5). Two patients showed signs of urticarial vasculitis characterized by erythrocyte extravasation, neutrophilic infiltration, endothelial swelling accompanied by nuclear debris, necrosis, and fibrin deposition with marked karyorexi (n=2).
Maculopapular eruption (n=7)	Superficial perivascular lymphocytic infiltration was accompanied by neutrophils and eosinophils. Lymphocyte exocytosis was observed in the epidermis.
Panniculitis (n=2)	Septal panniculitis consisting of lymphocytes, histiocytes, and eosinophils in the subcutaneous adipose tissue was detected in one patient. In another patient, findings consistent with nodular vasculitis were observed.
Purpuric eruption (n=2)	Histological examination of skin biopsy specimens from two patients with purpuric eruptions (n=2) showed mild-to-moderate spongiosis in the mildly hyperkeratotic epidermis. Leukocytoclastic vasculitis, characterized by dense neutrophilic infiltrate, nuclear debris, and fibrin extravasation, was detected in the dermis on the vessel walls and around the vessels.
Livedoid-like pattern (n=1)	Histopathologically, there was vascular dilatation and thickening of the vessel walls, endothelial hyperplasia, fibrin and erythrocyte extravasation, and mild perivascular inflammation in the superficial dermis.

urticarial vasculitis (n=7), maculopapular eruption (n=7), panniculitis (n=2), purpuric eruption (n=2), and livedoid-like pattern (n=1) (Figure 1A-F).

The histopathological examination of urticarial lesions revealed dermal edema, perivascular lymphocyte, and eosinophil infiltration (n=5). Two patients showed signs of urticarial vasculitis characterized by erythrocyte extravasation, neutrophilic infiltration, endothelial swelling accompanied by nuclear debris, necrosis, and fibrin deposition with marked karyorexia (Figure 2A, B).

In the histopathological examination of biopsy samples taken from maculopapular eruptions, superficial perivascular lymphocytic infiltration was accompanied by neutrophils and eosinophils. Lymphocyte exocytosis was observed in the epidermis.

Three of the seven patients with maculopapular rash also had signs of vasculopathy. A 5-year-old boy with a diffuse maculopapular rash on the whole body was diagnosed with MIS-C. In the histopathological examination of the skin biopsy taken from that child, perivascular lymphocytes, sparse plasma cells, and erythrocyte extravasation were observed in the superficial dermis. There were signs of vasculopathy such as vascular proliferation and endothelial hyperplasia (Figure 3A, B).

Septal panniculitis consisting of lymphocytes, histiocytes, and eosinophils in the subcutaneous adipose tissue was detected in one patient. In the other

patient, findings consistent with nodular vasculitis were observed. In the histopathological examination of this lesion that appeared as tender, erythematous nodules on the patient's leg, signs of vasculitis accompanying panniculitis were observed (Figure 4A, B).

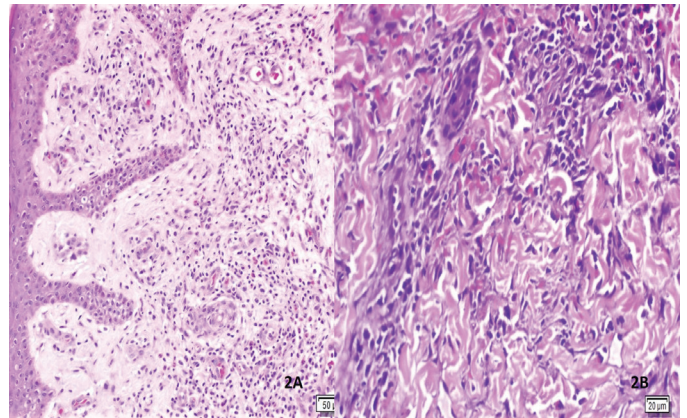


Figure 2. (A) Urticarial lesion, histopathologic picture. Dermal edema, perivascular lymphocyte and eosinophil infiltration (H&E, ×200). (B) Urticarial vasculitis morphology. It was characterized by erythrocyte extravasation, neutrophilic infiltration, endothelial swelling accompanied by nuclear debris, necrosis, and fibrin deposition with marked karyorexia. (H&E, x400).
H&E: Hematoxylin and eosin staining

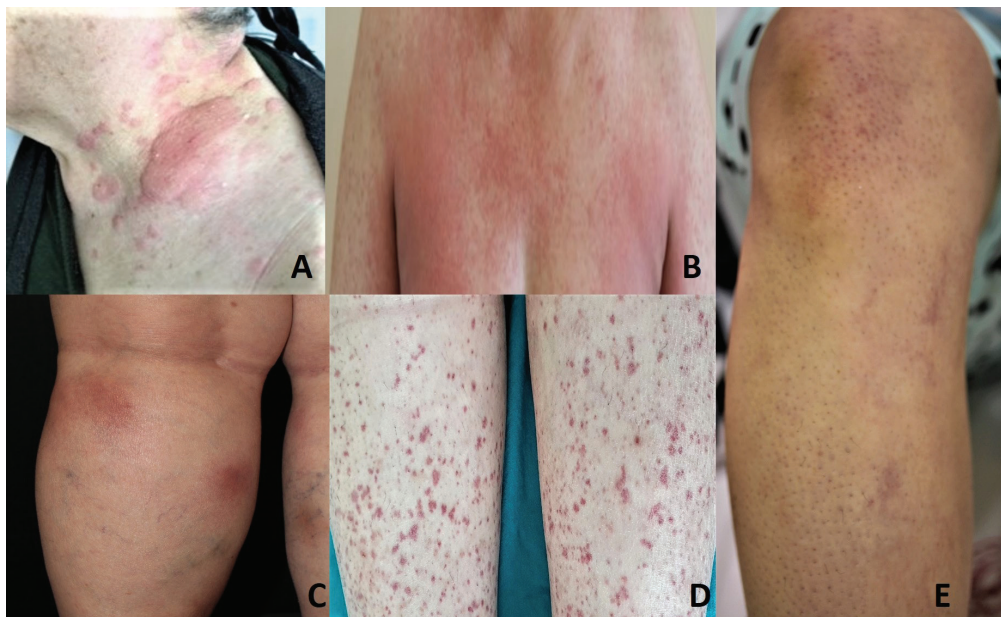


Figure 1. (A) Urticarial lesions, (B) maculopapular eruption, (C) panniculitis/nodular vasculitis, (D) purpuric eruption, and (E) livedoid-like lesion.

Histological examination of skin biopsy specimens from two patients with purpuric eruptions (n=2) showed mild-to-moderate spongiosis in the mildly hyperkeratotic epidermis. Leukocytoclastic vasculitis, characterized by dense neutrophilic infiltrate, nuclear debris, and fibrin extravasation, was detected in the dermis, vessel walls, and around the vessels. In the direct immunofluorescence examination of the skin biopsies of these patients, significant fibrinogen deposition in the vessel walls was observed (Figure 5A, B).

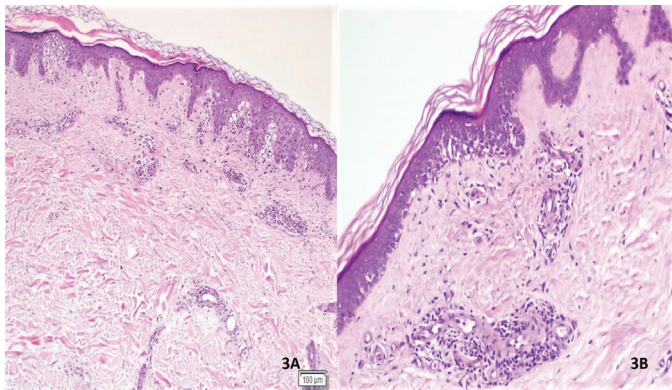


Figure 3. Maculopapular eruptions. In the histopathological examination of the skin biopsy taken from the child, perivascular lymphocytes, sparse plasma cells, and erythrocyte extravasation were observed in the superficial dermis. (A) H&E, $\times 100$, (B) H&E, $\times 200$.

H&E: Hematoxylin and eosin staining

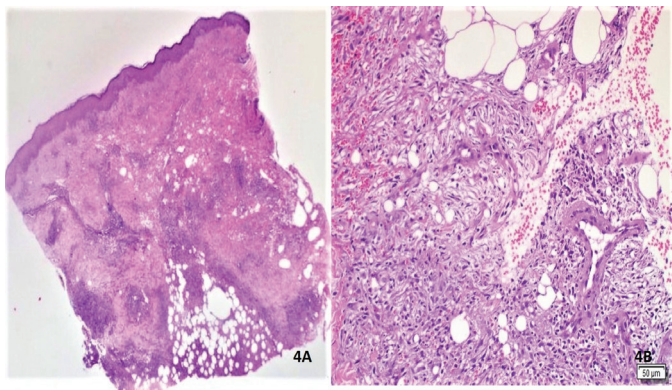


Figure 4. (A) Septal panniculitis consisting of lymphocytes, histiocytes, and eosinophils in the subcutaneous adipose tissue was detected in one patient (H&E, $\times 20$). (B) Nodular vasculitis; there were signs of vasculitis accompanying panniculitis (H&E, $\times 200$).

H&E: Hematoxylin and eosin staining

Two patients had livedoid-like rashes. Histopathologically, there were vascular dilatation and thickening of the vessel walls, endothelial hyperplasia, fibrin and erythrocyte extravasation, and mild perivascular inflammation in the superficial dermis (Figure 6).

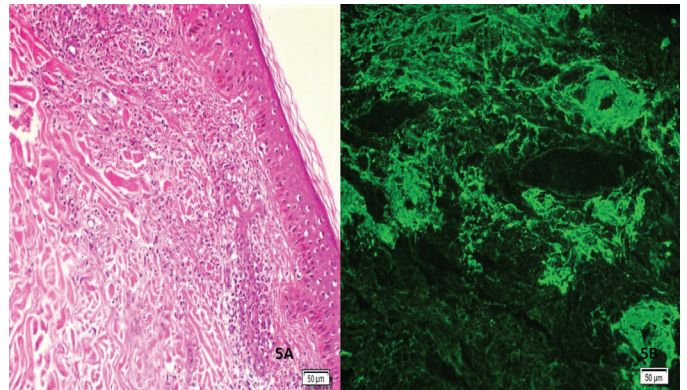


Figure 5. (A) Purpuric eruptions, histological picture. There were mild-to-moderate spongiosis in the mildly hyperkeratotic epidermis. Leukocytoclastic vasculitis, characterized by dense neutrophilic infiltrate, nuclear debris, and fibrin extravasation, was detected in the dermis on the vessel walls and around the vessels (H&E, $\times 200$). (B) Significant fibrinogen deposition in the vessel walls was observed (direct immunofluorescence antibody for fibrinogen, $\times 200$).

H&E: Hematoxylin and eosin staining

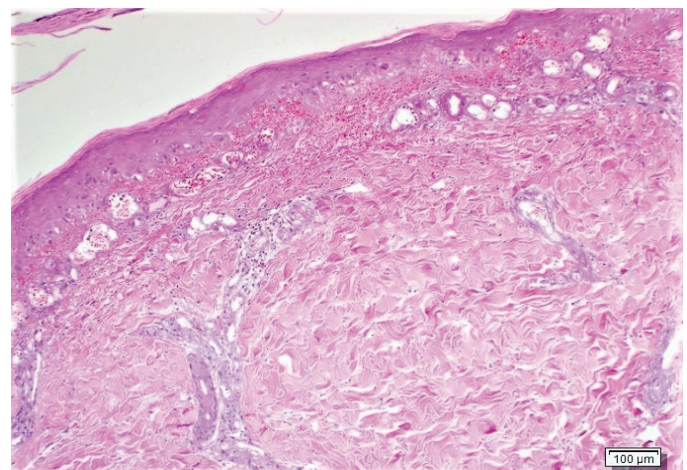


Figure 6. Histopathology of livedoid-like rash. There was vascular dilatation and thickening of the vessel walls, endothelial hyperplasia, fibrin and erythrocyte extravasation, and mild perivascular inflammation in the superficial dermis (H&E, $\times 100$).

H&E: Hematoxylin and eosin staining

In our patients with COVID-19, the most striking feature in the histopathological examination of skin biopsies was the systemic involvement of vascular structures.

DISCUSSION

Skin manifestations of COVID-19, which mostly manifests with respiratory findings, are rare. The pathogenetic mechanism of cutaneous manifestations of COVID-19 is not yet fully known. Some common theories are being discussed^{4,8}.

Although many theories have focused on this issue during the pandemic, there is no proven hypothesis yet⁶. Two main pathogenetic mechanisms are highlighted. The first of these is the immune response against viral nucleotides, as in many viral diseases, and the other are skin rashes that involve vascular structures because of the systemic effects of COVID-19. In some studies, SARS-like viral particles and SARS-CoV-2 RNA have been detected in T-lymphocytes and are involved in T-cell viral infection. It is also thought that the infection may increase proinflammatory cytokines immunopathologically, and these cytokines may cause lesions by stimulating inflammatory cells in the skin. A hyperactive immune response, complement activation, and microvascular injury have been implicated.

Various clinical manifestations are mentioned in many case reviews reported, such as maculopapular, papulovesicular, purpuric lesions, petechial lesions, urticaria, pityriasis lesions, livedoid lesions, ischemic lesions, erythema multiforme-like lesions, chilblain-like lesions, urticarial vasculitis, and panniculitis-like lesions¹¹⁻¹⁵. The clinical manifestations of the 19 cases presented herein consisted of urticaria, maculopapular eruptions, panniculitis, erythema multiforme-like eruptions, and livedoid-like lesions.

In their literature review, Sachdeva et al.⁴ stated that macular-maculopapular eruptions are the most common lesions. Urticarial and maculopapular lesions were observed most frequently in our cases.

Urticaria can be triggered by viral and bacterial agents. However, it may also occur against drugs taken for any reason. Sometimes, this distinction may not be possible⁶. Urticarial eruptions associated with COVID-19 have been reported at varying rates in various studies^{4,6}. In our study, five of the patients who developed urticaria had rashes simultaneous with other COVID-19 findings, and they did not have a history of using other drugs. One patient developed urticaria on the third day while receiving COVID-19 treatment (antiviral treatment).

Therefore, it is difficult to determine whether skin rashes are secondary to treatment. One patient was followed up for hematological malignancy, but he did not use drugs other than those he normally took. Histopathologically, mild edema, proliferation in small vessels, perivascular lymphocytes, and a few eosinophils were detected in the superficial dermis. In addition to the classical urticaria morphology, urticarial vasculitis findings were observed in two patients.

Erythematous/maculopapular/morbilliform rashes have been revealed as a very common finding in many review studies on cutaneous findings of COVID-19¹⁶⁻²¹. Histopathologically, in many studies, superficial perivascular lymphocytic infiltration and some vascular damage were reported in these lesions^{5,22-24}. In our study, extensive vasculopathy was observed in three of the seven patients with maculopapular and morbilliform eruptions. No evidence of active vasculitis was observed in these patients. One of these patients was a 5-year-old boy diagnosed with MIS-C. In two of the patients with maculopapular rash, rashes started just a few days before the onset of COVID-19 symptoms. In four patients, rashes occurred simultaneously with COVID-19 symptoms. In the pediatric patient with MIS-C, rashes occurred on the third day of treatment. Therefore, it is difficult to determine whether the rashes are caused by COVID-19 or drugs used in the treatment. The condition characterized by fever, systemic inflammation, multiorgan involvement, and often rash caused by coronaviruses in children is called MIS-C²⁵. Many studies have stated that MIS-C can cause rashes in children in various forms²⁵⁻³¹. Although skin findings are common in MIS-C, the underlying pathophysiology is not well understood yet. Thus, research with larger series of cases and perhaps molecular/immunological studies on this subject are necessary.

Many review studies have described a skin rash in a purpuric pattern in patients with COVID-19³²⁻³⁴. The purpuric pattern usually reflects the damage caused by the virus to vascular structures and is characterized by vasculitis³⁵⁻³⁷. These lesions, which are less reported, were also present in two patients analyzed in our study.

Until today, very few cases of panniculitis thought to be associated with COVID-19 have been reported. In their review, Kaya et al.¹¹ reported a case of lobular panniculitis presenting as eosinophilic panniculitis. Alanso et al.³⁸ reported a patient with non-eosinophilic panniculitis. In the present study, two patients, of which one had nodular vasculitis, were diagnosed with panniculitis. Neither had a known disease before. However, they were older patients and both had more severe COVID-19 symptoms.

Livedoid lesions were reported in 1 of 7 patients in a study conducted in France and 3.5% in the large case series of 716 patients by Freeman et al.³⁹. In the present study, livedoid lesions were detected in 1 of 19 patients (5.2%). This rate is high compared with those reported in other studies. This may be due to the difference in the number of patients analyzed in the studies or differences in genetic structures.

COVID-19, which continues with many unknowns, affects the skin and all body systems. Although many theories have been studied about the mechanisms of skin findings, many mechanisms are unexplained and unknown. Pathogenetic mechanisms such as deviations in immune response, vascular damage, and complement activation are being studied⁶.

In this small series, damage to vascular structures is one of the common histopathological features of the lesions. Although active vasculitis is seen in a few patients, most of them have signs of vasculopathy. It is thought that SARS-CoV, identified as the etiologic agent of SARS, acts through ACE-2. ACE-2 is also found in the basal layer of the epidermis, dermal vascular endothelial cells, and eccrine adnexal tissue⁴⁰. Thus, we should focus on this issue. However, the skin is involved in all kinds of infections and systemic diseases and is affected even by drugs.

CONCLUSION

Cutaneous lesions associated with COVID-19 are increasingly being reported. We believe that every data presented about this disease, which has many unknowns, will shed light on future research. Every case can lead us a new way.

Ethics

Ethics Committee Approval: The article was approved by the Istanbul Medeniyet University Goztepe Training and Research Hospital Clinical Research Ethics Committee with the number 2022/0233 (date: 13.04.2022).

Informed Consent: Informed consent was obtained from the patients.

Peer-review: Externally and internally peer-reviewed.

Author Contributions

Surgical and Medical Practices: B.C., F.C., M.S., S.O., Concept: B.C., S.O., Design: B.C., M.S., Data Collection and/or Processing: B.C., F.C., S.O., Analysis and/or Interpretation: B.C., F.C., S.O., Literature Search: B.C., M.S., Writing: B.C., M.S.

Conflict of Interest: The authors have no conflict of interest to declare.

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