Review Article

Histopathologic Changes and Cellular Events of Organs Systems in COVID-19

Niloufar Najar Nobari[1], Fatemeh Montazer[2], Farnoosh Seirafianpour[3], Farahnaz Nikkhah[4], Zeinab Aryanian[5,6], Azadeh Goodarzi[1*]

Abstract

A better understanding of histopathologic and cellular events of COVID-19 can help us to choose more proper management strategies and treatments. There are several ways to cellular and histopathologic evaluations; including, tissue sampling from living people as biopsies or dead people as autopsies or necropsies. In this study, we tried to evaluate the histopathologic concordance between findings of various tissue samplings derived from different sites that may work as a mirror of each other, especially mucocutaneous findings which may be indicative of similar events of other parts. Based on the main keywords, we searched databases of PubMed, Scopus, Google Scholar, Medscape, and CEBD coronavirus dermatology resource of Nottingham University and included the most relevant and well-designed studies with a higher level of pieces of evidence and higher sample size. In this study, selected pathological samples from different tissues of patients with COVID-19, including skin and mucosa, lungs, gastrointestinal tract, and kidneys were studied and summarized. Cellular changes and pathological findings in these patients were included by organ and listed by prevalence. Tissue sampling in patients with COVID-19 may help understand the pathophysiology of the disease as much as possible. Although most of these samples are taken after dying the patients, sampling before the more advanced stages of the disease could also show signs of tissue involvement before appearing the full systemic symptoms.

Keywords: Corona, COVID-19, Biopsy, Autopsy, Necropsy, Tissue sampling, Histopathology, Immunohistochemistry (IHC), Histology, Pathology

1. Department of Dermatology, Rasool Akram Medical Complex, Iran University of Medical Sciences (IUMS), Tehran, Iran
2. Department of Pathology, Firoozabadi Clinical Research Development Unit (FCRDU), Iran University of Medical Sciences (IUMS), Tehran, Iran
3. Student Research Committee, School of Medicine, Iran University of Medical Sciences (IUMS), Tehran, Iran
4. Rasool Akram Medical Complex Clinical Research Development Center (RCRDC), Iran University of Medical Sciences, Tehran, Iran
5. Autoimmune Bullous Diseases Research Center, Tehran University of Medical Sciences, Tehran, Iran
6. Department of Dermatology, Babol University of Medical Sciences, Babol, Mazandaran, Iran

Corresponding Author:
Dr. Azadeh Goodarzi, Department of Dermatology, Rasool Akram Medical Complex, Niayesh St. Sattarkhan Ave., Tehran, Iran.
E mail:
Azadeh_goodarzi1984@yahoo.com

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Introduction

In the pandemic era of COVID-19, it is important to know what happens in the disease course in different parts of our body. Involvement of each site could be a presenting sign of a new coronavirus with its special clinical symptoms, but "how we can access the real data in this regard?"

Tissue sampling evaluations of different organs- in living people as biopsies or in dead people as autopsies- give access to histopathological events during the COVID-19 course. To further improve our knowledge about the probable underlying

pathophysiology of affected tissues and taking a better approach to the treatment, it is needed to understand more about histopathological events. In COVID-19, skin biopsy of affected patients and primary viral-related cutaneous manifestation could be an appropriate diagnostic method; however, a biopsy of internal organs can be done under certain conditions but it is very rarely necessary and complex, and accompanied by legal ethical issues, while the autopsy of internal organs and their histopathological examination is much easier under the observance of ethical and legal rules that it is quite possible and acceptable.

Based on autopsies, COVID-19 is a systemic disease with major cardiovascular and pulmonary involvement in a cytokine storm and inflammatory setting, associated with a hypercoagulative state and susceptibility to microangiopathy and micro/macro thrombotic events (1).

Many efforts have been done to prepare autopsy guidelines per detail. Here, we would like to answer these questions regarding the COVID-19 course:

- Is skin biopsy somehow indicative or predictive of histopathological events of internal organs so to be considered as a substitute for internal organ biopsy, necropsy, or autopsy?
- Is skin biopsy indicative or predictive of histopathological events of internal organs? Is there histopathological concordance?
- Can tissue samples and pathological findings predict the course of the disease or the occurrence of expected clinical manifestations?

In the setting of pathologic concordance between data of various tissue samplings, perhaps the maximum biopsy of all available cases with affected skin is a good reason to raise our knowledge regarding the pathogenesis of the disorder. This is what we tried to approach in this comprehensive review.

We searched databases of PubMed, Scopus, Google Scholar, Medscape, and CEBD coronavirus dermatology resource of Nottingham University (https://www.nottingham.ac.uk/). Our keywords were ("COVID-19") OR ("severe acute respiratory syndrome coronavirus2") AND ("Skin") OR ("Cutaneous") OR ("Mucosa") OR ("Appendageal") OR ("Skin Manifestations") OR ("Dermatology") OR ("Pathology") OR ("Histology") OR ("Histopathology") OR ("Histopathologic") OR ("Histology") OR ("Biopsy") OR ("Autopsy") OR ("Necropsy"). For writing this comprehensive review, we included the most relevant, large (higher sample size) and well-designed studies with a higher level of evidence. The date of our search was from January 2020 to June 2020. We searched these databases for articles including data of patients who died from COVID-19 and being undergone autopsies for histopathological evaluation of different vital internal organs especially the lung, heart, and liver. In our search, we also found a living patient who was assessed after lung transplantation for histopathologic changes of the extracted lungs. We tried to discuss pathological events in different parts of the dead people and compare the histopathological findings between various organs even mucocutaneous changes. We focused on similarities or discrepancies for future better judgments about real COVID-19 pathogeneses as well as the events that may lead to different organ failures or death.

In this review, we focused on some main categories of histopathologic evaluations in COVID-19 patients; such as mucocutaneous and skin appendage histopathologic findings primarily related to the virus itself (not to its therapy (adverse cutaneous drug reactions)), pulmonary and other internal organ tissue sample or biopsy's histopathologic data and also the histopathologic changes and features in various sites of autopsies (2-20). The findings of the articles are reviewed and the results are presented in the order of prevalence in the table below (Table 1).

Novel coronavirus pneumonia caused by SARS-CoV-2 has a worldwide outbreak since it firstly occurred in December 2019, Wuhan city, China (21, 22). It was reported that the virus homology was over 85% between novel coronavirus pneumonia and severe acute respiratory syndrome (SARS). It means that the pathological changes of COVID-19 might be similar to SARS patients (23). In various tissue samples taken from patients with COVID-19, various manifestations can be observed depending on the involvement of the tissue and clinical symptoms. Using histology in these patients may raise our understanding of the pathophysiology of the COVID-19 virus. Histological studies in these patients mostly include

Table 1: COVID-19-induced histopathologic changes in biopsy or autopsy samples of different sites.

Mucocutaneous pathology	• Sub corneal pustules • Spongiosis • Papillary dermal edema • Perivascular and interstitial inflammatory cells infiltration consist of neutrophil and eosinophil • Erythrocyte extravasation • Microthrombi /fibrin thrombi • Vasculitis (usually necrotizing rather than lymphocytic) • Necrosis of the epidermis and dermis • Vacuolar degeneration of the basal layer • Lichenoid dermatitis • Lymphocytic exocytosis to the epidermis and acrosyringia • Dyskeratotic cells/ ballooning multinucleated keratinocytes • Superficial vascular ectasia (Blue: epidermal changes, Green: dermal changes)
Pulmonary pathology	• Bilateral diffuse alveolar damage (DAD) • Proteinaceous exudate • Pneumocyte hyperplasia • Hyaline membrane formation • Syncytial giant cell forms • Interstitial fibrosis • Vascular lumen stenosis • Micro thrombosis formation • Alveolar cavity congestion • Desquamation and squamous metaplasia in alveolar epithelial cells • Inclusion of viral bodies
Cardiac Pathology	• Mild lymphocytic myocarditis • Epicarditis • Focal mild fibrosis • Mild myocardial hypertrophy • Interstitial fibrosis
Liver Pathology	• Periportallymphoplasmacytic infiltration • Micro vesicular steatosis • Centrilobular sinusoidal dilation

	• Patchy hepatic necrosis • Fibrosis • Nuclear glycogenetic in hepatocytes • A mild increase in sinusoidal lymphocytes • Kupffer cells hyperplasia in few sinusoidal spaces
Splenic pathology	• Diminished white pulp with loss of marginal zones • Expansion of red pulp with lymphoplasmacytic infiltrate
Placental pathology	• Thrombosis • Intramural fibrin deposition • Villous stromal-vascular karyorrhexis • High-grade chronic villitis with associated avascular villi (obliterative vasculopathy) impaired vascular perfusion • Decidualvasculopathy • Acute chorioamnionitis and funisitis • Meconium-stained amniotic fluid and **meconium** macrophages • Basal chronic villitis • Hypercoiled umbilical cord, distal villous immaturity • Funisitis • Retroplacental hematoma • Cord hemangioma
Renal pathology	• Loss of tubular brush border • Vacuolar degeneration of the tubular epithelium • Dilatation of the tubular lumen with cellular debris • Necrosis and detachment of tubular epithelium • Hemosiderin granules in tubular epithelium • Lymphocytic infiltration subcapsular areas • Pseudo crescent appearance in glomerular structure

mucocutaneous, lung, liver, and kidney biopsies. Many of these findings have been derived from post-mortem sampling. Skin manifestations are also abundant in these patients, ranging from viral exanthema to vascular manifestations. Skin lesions may occur at any stage of the disease from asymptomatic carriers to patients admitted to the intensive care unit (ICU). Biopsy of these lesions shows different cases that correspond to the bed, such as Microthrombi/ fibrin thrombi, vasculitis, necrosis of the epidermis and dermis, and lichenoid changes. The lungs of the patients involved with COVID-19 showed diffuse alveolar damage and infiltrating perivascular lymphocytes with diffuse congestion and hemorrhagic necrosis, proliferative bronchiolitis, and alveolitis with pneumocytes proliferation, alveolar epithelial atrophy, epithelial desquamation, and squamous metaplasia. Similar changes in association with vascular damages

include various degrees of inflammatory reactions and host immune reaction with variable tissue damages, like those seen in skin and lung biopsies, that all may be observed in other organs, such as the liver and kidneys. Examination of the pathological changes in the tissue can predict the manifestations of the disease and its course (24). Although most of these tissue samples especially from the lungs, liver, or kidneys have been prepared since the patient's death, evidence of the tissue involvement can be effective in the judgment of the disease.

Mucocutaneous findings are prevalent in COVID patients and studies report that about 20% of the patients have viral associated dermatologic signs that most of them are clinically compatible with maculopapular exanthematous or urticarial rash and vasculopathy or vasculitic features specially COVID Toes (8, 25-28). Histology findings along with viral affected pathologic changes and nonspecific inflammatory reactions indicate that an important group of patients have thrombotic microvascular events that are related to certain clinical presentations and laboratory hypercoagulative states in some patients (12, 29, 30).

A whole-lung biopsy of a patient who developed acute respiratory distress syndrome (ARDS) and respiratory failure and underwent lung transplantation showed diffuse congestion some hemorrhagic necrosis in the tissue. Gross examination and serial cuts microscopic histopathologic evaluation showed proliferative bronchiolitis and alveolitis with Pneumocytes hyperplasia, atrophy of alveolar epithelium, epithelial desquamation, and squamous metaplasia as well as massive fibrosis with hyaline degeneration and various stages of hemorrhagic infarction. Massive fibrosis is confirmed by Masson staining. The proliferation of thickened wall small vessels, luminal stenosis, occlusion, and micro-thrombosis was another main finding. Monocytes, lymphocytes, and plasma cells were infiltrated focally to the lung. Infiltrating into the pulmonary interstitium, and Immunohistochemistry (IHC) showed CD3, CD4, CD8, CD20, CD79a, CD5, CD38, and CD68 positive immune cells. Alveolar epithelial cells showed atrophy, vacuolar degeneration, proliferation, desquamation, and squamous metaplasia, and the alveolar cavity was congested and filled by mucus, edema fluid, desquamated epithelial cells, and various degrees of inflammatory cells. Multinucleate giant cells and intracytoplasmic and intranuclear viral inclusion bodies (as viral cytopathic effect) also were found. In the COVID-19 course, several representative cytokines have been identified including IL-1β, IL-18, TNF-α, IL-6, IL-8, and IL-10, which are produced and regulated by various immunological cells including CD8 and CD4 T cells (31).

There are many articles regarding autopsies of internal organs in COVID-19 patients, especially pulmonary, cardiac, and liver samples. In the lung, cytopathic effects usually with no obvious intranuclear or intracytoplasmic viral inclusions could also be identified as multinucleated syncytial cells with atypically enlarged pneumocytes characterized by large nuclei, amphophilic granular cytoplasm, and prominent nucleoli in intra-alveolar spaces. Fibrotic pathogenic events during systemic involvements in COVID-19 may be seen, especially in the lung. Moreover, important proteinaceous exudates as large protein globules, vascular congestion accompanied by inflammatory clusters of fibrinoid materials, multinucleated giant cells; pneumocyte hyperplasia and bilateral diffuse alveolar damage (DAD) with cellular fibromyxoid exudates also may be observed. Also, desquamated pneumocytes and hyaline membrane formation, suggesting interstitial mononuclear inflammatory infiltrates, were reported in ARDS dominated by lymphocytes (32, 33).

In postmortem needle core biopsies of the lung, liver, and heart of four patients who died of COVID-19 pneumonia, the main histopathologic finding of the lung was diffuse alveolar damage (DAD), including injury to the alveolar epithelial cells, hyaline membrane formation, and pneumocytes type II proliferation. Fibrotic degeneration consists of fibroblastic proliferation with the extracellular matrix, and fibrin cluster formation in airspaces was found. In the case of high intra-alveolar neutrophilic infiltration, there was bacterial superinfection. Changes in the liver and heart are likely secondary or related to the underlying diseases or are drug-dependent (especially in liver histopathological changes). The liver exhibited mild lobular infiltration by small lymphocytes, and centrilobular sinusoidal dilation along with patchy

necrosis, and the heart showed only focal mild fibrosis and mild myocardial hypertrophy (34).

The most important findings of recent studies indicate that the pulmonary small vessel and capillary thrombosis and microangiopathy with associated hemorrhage can be probably the main cause of the death. Severe endothelial injury associated with the presence of the intracellular virus and disrupted cell membranes and widespread thrombosis with microangiopathy could a characteristic feature of the lung involvement in COVID-19; so that alveolar-capillary microthrombi could be 9 times more prevalent than that in patients with influenza, and new vessel growth (intussusceptive angiogenesis) could be 2.7 times more prevalent than that in patients with influenza.

DAD including hyaline membrane formation could be seen in all patients, even non-intubated ones, and it is similar to histopathologic features of coronavirus as a severe acute respiratory syndrome (SARS). In the heart, individual cell necrosis without lymphocytic myocarditis is the most characteristic finding. Secondary pulmonary infection by microorganisms is of great concern nowadays. Central Nervous System did not show any involvement (2, 34, 35).

Although viral inclusion bodies in lung autopsies are not usual in an autopsy sample from Iran, we observed intra-alveolar hemorrhage, moderately interstitial inflammation composed of lymphocytes, plasma cells and neutrophils, focally necrosis and alveolar destruction, intravascular micro-thrombi, and large multinucleated pneumocytes with the focal presence of intranuclear inclusion like structure (maybe due to viral cytopathic effect), desquamation of pneumocytes without any evidence of mucus plugging within airways. Furthermore, in the liver autopsy of another case from Iran, we observed mild lobular and portal inflammation dominated by lymphocytes, moderate macrovesicular and mild microvesicular steatosis with diffuse distribution, moderate ballooning degeneration of hepatocytes with moderate bile pigment (36).

Due to the somewhat histopathological similarity between the involvements of different organs, it is important to know" which organ or organs are the main targets of the COVID-19 virus?"

Since most of the severe complications and deaths caused by the virus are due to lung involvement, so the lung can be the main target of the virus and other organs may be involved secondarily; however, they could act as a good predictor of pathologic events in the main target organ. Skin is the best example with more evident and accessible data among these secondary organs (37).

However, some facts about the actual course of COVID-19, the sequels, prognostic factors, treatments, and the manner of different parts of the body involvement would become clearer in the future, and the field of dermatology is not an exception. Some concerns are of great importance and need further investigation, including The virus-related or drug-related mucocutaneous signs of COVID-19 (38), management of patients with a specific dermatologic disorder in the pandemic era (39), or approach to the elective therapies especially in the elderly patients (40) like cosmetic procedures, non-emergent surgeries, or some chronic insignificant medical skin disorders (41), and more focus might be given to teledermatology.

The field of COVID is of interest to the authors of this review, and they are interested in COVID-19 issues in various fields especially COVID-19 and dermatology and now they think this topic may a valuable concern to discuss (42-45). In the pandemic era, there are many concerns about prevention, early diagnosis, and treatment of patients with COVID-19 (46-48) so here we tried to focus on a hot topic that may help to increase our knowledge about probable pathomechanisms that results to design better management protocols.

Conclusion

This study doubles the importance of tissue sampling. First, it helps to know more about the pathophysiology of the disease and how different tissues are involved. Second, it may be effective in predicting the course of the disease and subsequent clinical manifestations.

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Conflicts of Interest

The authors declare that there are no conflicts of interest.

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