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DERLEME
REVIEW

Pathological features of COVID-19 infection from biopsy and autopsy series

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ABSTRACT

Pathological features of COVID-19 infection from biopsy and autopsy series

Novel coronavirus disease 2019 (COVID-19) which is caused by severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) was first identified in December 2019 in Chinese town Wuhan and considered as a pandemic by World Health Organization. The disease has variety of symptoms including fever, shortness of breath, cough, fatigue, loss of smell and taste and diarrhea. While the majority of cases have mild symptoms, some progress to viral pneumonia, multi-organ failure, or cytokine storm and mortality is mostly caused by hypoxemic respiratory failure. Until now, more than 3.5 million people worldwide were infected and more than 240.000 mortality has been occurred. Thus, there is now evidence the disease may affect variety of organs according to accumulating biopsy and autopsy studies. Such pathological studies have potential role on the understanding of clinical outcomes and in the development of novel targeted therapeutic approaches. Given these aforementioned data, in the current manuscript we have summarized the pathological features of COVID-19 derived from biopsy and autopsy series.

Key words: COVID-19; lung injury; kidney injury; heart injury; biopsy; autopsy

ÖZ

COVID-19 enfeksiyonunun otopsi ve biyopsi raporlarına göre patolojik özellikleri

Yeni koronavirüs 2019 hastalığı (COVID-19) akut respiratuvar sendromu koronavirus 2 (SARS-CoV-2) ilk olarak Çin'in Wuhan şehrinde aralık 2019 tarihinde saptanmış olup, dünya sağlık örgütü tarafından pandemi olarak kabul edilmiştir. COVID-19 enfeksiyonu ateş, nefes darlığı, öksürük, halsizlik, ishal,

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koku ve tat alma bozukluğu gibi şikayetlere neden olabilmektedir. Hastalık yüksek oranda asemptomatik geçirilse bile bazı hastalarda viral pnömoni, solunum yetmezliği, çoklu organ yetmezliği ve sitokin fırtınası gelişebilmekte ve ölüme neden olabilmektedir. Şimdiye kadar 3.5 milyonun üzerinde insan enfekte olmuş olup, 240.000 üzerinde insan ölmüştür. Biyopsi ve otopsi raporlarında akciğer dışı birçok organında tutulduğu gösterilmiştir. Bu bilgilerin yeni tedavi modalitelerinin gelişmesine yardımcı olabileceği ümit edilmektedir. Bu derlemede COVID-19 enfeksiyonu olan hastalarda yapılmış biyopsi ve otopsi raporlarında covid enfeksiyonuna bağlı organ tutulumları ve tipleri detaylıca tartışılmıştır.

Anahtar kelimeler: COVID-19; akciğer hasarı; kalp hasarı; böbrek hasarı; otopsi; biyopsi

INTRODUCTION

As third recent outbreak of Coronaviruses family following severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) viruses, coronavirus disease 2019 (COVID-19) pandemic has originated in a Chinese town Wuhan in December 2019 and infected more than 3.5 million people worldwide with more than 240.000 mortality so far (1). Most common clinical presentation features include fever (88.5%), cough (68.6%), fatigue (35.8) and dyspnea (21.9%) as reported by a meta-analysis study involving 1995 cases while fatality rate is around 5% with predominant cause of mortality being acute respiratory failure (2). 20.3% intensive care unit admission requirement has been demonstrated in another meta-analysis involving 656 patients while 88% of ICU-admitted patients required respiratory support (3,4). Primary mode of transmission is through respiratory droplets while fecal-oral transmission has been implicated in few studies (5). Entrance of viral particles into pneumocytes and bronchial epithelial cells, primary sites of involvement, is mediated via interaction between angiotensin converting enzyme (ACE)-2 receptors and a protein domain with SARS-CoV cellular binding spike (6). Older age, presence of comorbid diseases and secondary infections, elevated inflammatory markers, high d-dimer and cardiac troponin levels, higher Sequential Organ Failure Assessment (SOFA) score and low T-cell count are shown to be statistically significant predictive factors for mortality (7,8). Currently there is no vaccine or medication approved by Food and Drug Administration (FDA) except emergency use approval for remdesivir, a RNA-dependent RNA polymerase inhibitor, despite few studies demonstrating inefficiency in COVID-19 treatment (9,10). In this study, we aim to evaluate the current knowledge about the pathological features of COVID-19 infection at organ systems on biopsy and autopsy samples and possible discuss the rationale behind new therapeutic trials.

PULMONARY SYSTEM

Acute respiratory failure, followed by fulminant myocarditis, is the most common cause of mortality in COVID-19 infected patients. High rate of respiratory and cardiovascular (CVS) involvement is believed to be linked to higher expression of ACE-2 receptors at that tissues (11). Respiratory symptoms are more severe in patients with comorbid CVS disorders and diabetes mellitus, presumably due to higher expression of ACE-2 receptors, which leads to hypothesis that use of ACE inhibitors (ACEi) and/or angiotensin-receptor blockers (ARB) may lead to higher susceptibility towards COVID-19 infection and poor clinical outcome (12-14). However, current evidence does not support abandonment of ACEi/ARB therapy in hypertension. In addition to being most commonly involved site in COVID-19 infection with symptoms including fever, dyspnea and cough, various laboratory, imaging and pathological findings have been demonstrated. Most common findings observed on chest X-ray studies are bilateral infiltration and ground-glass opacities while most common laboratory findings are elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), lymphopenia, hypoalbuminemia and high lactate dehydrogenase (LDH) levels (15). Pathological findings obtained from infected patients are consistent with diffuse alveolar damage (DAD) and early-phases of acute respiratory distress syndrome (ARDS). Viral particles have been obtained from respiratory tract epithelium and type II pneumocytes while contradictory findings have been reported regarding the presence of viral inclusions at respiratory cells. Main pathological findings include necrosis at respiratory epithelium, focal interstitial thickening and fibrosis, congested and edematous blood vessels, high amount of protein-rich inflammatory infiltration containing predominantly monocytes, macrophages and lymphocytes. Findings about hyaline membrane formation and intra-alveolar hemorrhages are inconclusive. General pathological features obtained on biopsy and autopsy samples are

summarized at Table 1. Similarities of COVID-19 infection and ARDS raise the possibility of immunotherapy use in the treatment. Tocilizumab, an IL-6 receptor antagonist approved in the treatment of cytokine release syndrome by FDA, is one such option for which clinical trials are ongoing since elevated levels of interleukin (IL)-2, IL-6, IL-10, tumor

necrosis factor (TNF) and interferon-gamma (IFN- γ) are reported at infected individuals (16,17). Melatonin, an anti-inflammatory and anti-oxidant molecule shown to reduce acute respiratory stress caused by pathogens, is hypothesized to have beneficial effects in the control of DAD and ARDS that developed in the course of COVID-19 infection (18). Similarly,

Table 1. Pathological findings of COVID-19 infection on biopsy and autopsy series in accordance with organ systems.

Organ systems	Pathological findings on biopsy and autopsy
Pulmonary system (58-69)	Edema with protein-rich exudate and patchy inflammatory infiltration predominantly including macrophages and monocytes Focal reactive hyperplasia of type II pneumocytes and multinucleated giant cells with nuclear atypia Inconsistent findings regarding hyaline membrane formation, intra-alveolar hemorrhages and intracytoplasmic viral inclusion bodies Congested, edematous and widened vessels around alveoli Necrosis of bronchiolar wall and epithelial cells (Consistent with necrotizing bronchiolitis) Focal interstitial thickening and fibrosis Mild to none effusion or adhesion Consistent with diffuse alveolar damage and early phase of ARDS
Heart (60-62, 66)	Mild to none interstitial mononuclear inflammatory infiltrates Dilatation especially at right ventricle Focal myocardial necrosis
Kidney (38, 39, 70, 71)	Diffuse and prominent proximal tubular injury including brush border loss, vacuolar degeneration with varying size and focal necrosis Effacement of foot processes at podocytes Presence of hyaline casts Obstructed capillaries with RBC aggregates without platelets or fibrin plugs Upregulation of ACE2 receptors on immunostaining Crescentic proliferative glomerulonephritis Collapsing glomerulopathy Mild to none inflammatory or lymphocytic infiltration Consistent with AKI and ATN
Liver (60-62, 69)	Moderate microvesicular steatosis, centrilobular steatosis, mild sinusoidal dilatation Mild to none inflammatory or lymphocytic infiltration
Spleen (59, 61, 72)	Decline in lymphocyte follicles and count including B and T-cells No difference in NK cell count Necrosis of parenchymal cells Hyaline thrombus formation at small vessels Atrophy at pulps
Skin (53, 59, 73-76)	Edema with diffuse lymphocytic infiltration predominantly at perivascular area and dermis Focal areas of spongiosis, necrosis and basal cell vacuolization Thrombogenic vasculopathy
CNS (61)	No gross abnormality
GIS (61)	No gross abnormality except increased fatty infiltration
Genital system (61)	No gross abnormality
Endocrine system (61)	No gross abnormality
Musculoskeletal system (61)	No gross abnormality
Abbreviations: ACE: Angiotensin converting enzyme, RBC: Red blood cell, NK: Natural killer, ARDS: Acute respiratory distress syndrome, AKI: Acute kidney injury, ATN: Acute tubular necrosis.	

Chimeric Antigen Receptor T Cell Therapy (CAR-T), plasma therapy, immunoglobulin therapy, thymosin, corticosteroids, anakinra (IL-1 receptor antagonist), immunoglobulin Fc domains, siltuximab (IL-6 antagonist) and many others have been implicated (19-21). Furthermore, another hypothesis based on similarity between COVID-19 infection and high altitude pulmonary edema in terms of clinical, laboratory and pathological features suggest potential use of acetazolamide, nifedipine and phosphodiesterase inhibitors such as sildenafil and tadalafil (22).

CARDIOVASCULAR SYSTEM and KIDNEY

Common cardiovascular comorbidities of COVID-19 infection include acute myocarditis, myocardial injury, acute myocardial infarction (AMI), acute heart failure and cardiomyopathy, thromboembolism and arrhythmia (23-25). 7-17% of hospitalized patients and 22-31% of ICU-admitted patients show elevated high sensitive troponin levels with mononuclear cell infiltration at myocardium on pathological samples which is consistent with acute myocarditis (26,27). Additionally, elevated pro-inflammatory cytokines and severe systemic inflammation markers have been associated with AMI (28,29). Although direct link between AMI and COVID-19 infection has not been established so far, strong hypothesis exists regarding the increased risk associated with viral infections including Influenza in earlier studies (30). Most commonly reported arrhythmia is sinus tachycardia and most likely have multifactorial etiology including pro-inflammatory status, hypoxia and fever (31). Another important CVS aspect of COVID-19 infection demonstrated on few case reports which may be caused by pro-inflammatory status, prolonged immobilization, dysfunction at coagulation cascade and multi-organ failure (32,33). In a retrospective study conducted with 191 patients d-dimer levels above 1 µg/mL has shown to be associated with increased mortality (34). Supporting evidence is demonstrated by a study conducted with 499 patients from which 99 patient received low dose heparin for at least 7 days that shows beneficial effects of low dose heparin administration on survival in patients with d-dimer greater than six times the upper limit of normal (35). Autopsy and biopsy studies investigating cardiac findings are limited in number while most common findings are mild including ventricular dilatation, focal myocardial necrosis and inflammatory infiltration (Table 1).

Elevated baseline serum creatinine, blood urea nitrogen, AKI, proteinuria and hematuria are identified as independent risk factors for in-hospital deaths according to a prospective cohort study including 701 patients (36). High rates of kidney involvement has been implicated in the course of COVID-19 infection. 65.8% proteinuria and 41.7% hematuria rates have been demonstrated in a study conducted with 333 infected patients while such high rates are seen in the course of many critical illness (37). However, rates of acute kidney injury (AKI) (7.5%) is considerably high compared to other illnesses suggesting direct viral involvement. Viral particles have been detected at tubular epithelium. Effacement of podocytes foot processes, prominent proximal tubular injury including loss of brush borders, necrosis and vacuolar degeneration, upregulation of ACE-2 receptors and obstructed capillaries with RBC aggregates without platelets or fibrin plugs are key pathological findings (Table 1) which is consistent with an AKI developing as a result of acute tubular necrosis (ATN). It was also shown that covid-19 may cause collapsing glomerulopathy or crescentic proliferative glomerulonephritis resulting in acute kidney injury (38,39).

LIVER, SPLEEN and GASTROINTESTINAL SYSTEM

Primary sites of involvement at COVID-19 infection in gastrointestinal system are liver, gastrointestinal tract and spleen. Most commonly encountered gastrointestinal symptoms in the course of COVID-19 infection are anorexia (39.9-50.2%), diarrhea (2-49.5%), vomiting 3.6-66.7%), nausea (1-29.4%), abdominal pain (2.2-6.0%) and gastrointestinal bleeding (4-13.7%) (40). 39.4% of patients have elevated aspartate aminotransferase (AST) and 28.1% have elevated alanine aminotransferase (ALT) level in a study from China conducted with 1099 patients (Median age= 47, 27% with at least one comorbid disorder) while most elevations are mild and not associated with liver failure or cholestasis (41). Similar abnormal liver function tests have been reported in multiple studies (42-44). Pathological features of COVID-19 infection at liver include moderate microvesicular steatosis, centrilobular steatosis and mild sinusoidal dilatation while inflammatory alterations and infiltration are mild. Possible mechanism of liver injury includes direct viral replication at hepatocytes which have considerable ACE-2 receptor expression, hypoxic injury in response to respiratory failure, immune-mediated damage, drug-induced

liver injury in response to multiple anti-viral and anti-inflammatory therapy and reactivation of pre-existent disease such as hepatitis B reactivation in response to tocilizumab therapy (45-47). Glycyrrhizic acid, an anti-inflammatory drug used in liver diseases for many years, have been proposed as a potential medication to manage liver dysfunction along with ACE-2 signaling pathway modulators including ACE-2/Ang-II/Mas signaling pathway activators and ACE-2/Ang-II/AT1R pathway inhibitors (48,49).

Another important site of COVID-19 infection is spleen, important regulator and center of immune system, in which viral particles are demonstrated. Pathological findings at spleen include decline in lymphocytes including cytotoxic T-cells, helper T-cells and B-cells, atrophy at white and red pulps, parenchymal necrosis and thrombus formation at small-sized vessels. Only major abnormality reported at gastrointestinal tract is increased adipose tissue infiltration while viral particles are demonstrated at intestines. General pathological features obtained on biopsy and autopsy samples are summarized at Table 1.

OTHER ORGAN SYSTEMS

Skin manifestations of COVID-19 are poorly described while various inflammatory (ie. exanthema, chicken-pox like vesicular lesions, urticaria) and vascular lesions (ie. livedo, necrotic and non-necrotic purpura, chilblain, eruptive cherry angioma) have been reported in retrospective studies (50-54). Most common site of involvement is trunk. Analysis of clinical manifestation of 1099 patients revealed that only 0.2% incidence of skin rash while incidence rates are considerably higher in more recent studies (55,56). Additionally, COVID-19 infection has been hypothesized as potential trigger for new onset or worsening of rheumatologic skin diseases similar to other members of Coronaviruses family but not yet proven (57). Drug-induced alterations, microvascular injury, immune system over-activation and secondary viral infections with mostly Herpesviruses family including Herpes simplex virus (HSV) and Varicella Zoster virus (VZV) have been proposed as potential etiological factor for skin manifestations while skin biopsy findings are correlated with viral infections (Table 1). Predominant features on skin biopsy samples are perivascular and dermal lymphocytic infiltration, microvascular thrombosis and vacuolar degeneration.

Until now no pathological abnormality on biopsy and autopsy samples have been recorded in musculoskeletal system, endocrinological system, genital system and central nervous system.

CONCLUSIONS

Although COVID-19 is a recent infection, the health, economic and social impact of the disease cannot be ignored due to its high infectious rate and relatively higher mortality. COVID-19 affected more than 185 countries which is the reason that the World Health Organization designate is as pandemic. New studies are coming up regarding the biopsy and autopsy findings of COVID-19 and it seems that various organs are affected (ie. lungs, heart, kidney, gastrointestinal system and skin). The most commonly affected organs are lungs and followed by heart and kidneys with various pathological findings. However, the data is only at infancy and it is probable that future studies will be able describe more about the pathological findings related with COVID-19 which is crucial for the development of targeted therapeutic options.

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