

Histopathologic findings in COVID-19 Autopsies from IRAN: A comprehensive report of laboratory, chest Computed tomography (CT) and morphology findings

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Abstract

Background: Coronavirus disease 2019 (COVID-19) is associated with diffuse alveolar damage (DAD) and coagulopathy in severe ill patients. Objective: To better understand and disease management, we investigated postmortem needle biopsies of lung, liver, and kidney pathologic changes along with clinical course, hematologic and imaging findings in two COVID-19 decedents. Patients and method We examined pathology of two patients with confirmed positive SARS-CoV-2 test died from respiratory failure. Computed tomography (CT) of the chest, Clinical and laboratory findings were investigated. Postmortem needle biopsies of lung, liver, and kidney were performed with complete protection. Results: The patients died from acute respiratory distress syndrome (ARDS). One of the patients was 56-year old man without any predisposing factor and the other (83-year old man) had hypertension, diabetes mellitus and renal failure. The patients had lymphopenia, elevated C-Reactive Protein (CRP), ferritin and D-Dimer. Axial CT images show diffuse ground glass opacity with some crazy paving and consolidation. The main pathologic finding of lungs revealed DAD. Intravascular micro-thrombi were detected despite anticoagulant prophylaxis. Renal autopsy demonstrated acute tubulointerstitial nephritis (ATIN) with tubular epithelium attenuation. Liver biopsy was consisted of lobular and portal inflammation and steatosis Conclusion This study emphasis that diffuse alveolar damage and microvascular pulmonary thrombosis in SARS-CoV-2 patients caused by either direct viral cytopathic effect or host immune and inflammatory reaction. Due to severe hypoxemia in COVID-19 patients suffering ARDS, appropriate oxygen support and anticoagulation therapy with strict monitoring is recommended

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Contributions

Fatemeh Montazer contributed pathologic examination

Alireza Almasi Nokiani performed Autopsy Procedures and chest CT scan interpretation,

Majid Rezaei Tavirani, Seyed Ali Javad-Movavi and Saeed Golami Gharab contributed in data collection

Mohammad Amin Abbasi and Farshad Divsalar contributed to study design and drafted manuscript

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Conclusion

This study emphasis that diffuse alveolar damage and microvascular pulmonary thrombosis in SARS-CoV-2 patients caused by either direct viral cytopathic effect or host immune and inflammatory reaction. Due to severe hypoxemia in COVID-19 patients suffering ARDS, appropriate oxygen support and anticoagulation therapy with strict monitoring is recommended.

Key words: COVID-19, diffuse alveolar damage, biopsy, thrombosis

It is known that ARDS and respiratory failure is the main cause of hypoxia and death in COVID19 patients.

What this article adds:

Fir st, this is the first AUTOPSY report of lung, liver and kidney from IRAN.

Second, besides DAD there was intra vascular micro thrombi although the patients were under anticoagulant therapy.

Third, cytopathic effect of virus might be considered.

Introduction

World Health Organization reported COVID-19, caused by novel coronavirus infection SARS-CoV-2, as pandemic in March 2020 which first distinguished in Wuhan, China in December 2019 and rapidly spread worldwide (1,2).

COVID-19 is associated with different clinical symptoms from mild asymptomatic infection to severe systemic inflammation result in acute respiratory distress syndrome (ARDS), myocarditis and severe COVID-19 sepsis (3-5).

Host hyper-inflammatory and hyperimmune responses in severe COVID-19 patients is associated with Diffuse alveolar damage (DAD), local endothelial cell dysfunction severe thrombo-inflammatory processes, vasculopathy and small vessel thrombosis (6,7). DAD is histological characteristic for the acute phase of ARDS and defined as presence of hyaline membranes (8).

Despite several studies focused on clinical manifestations of COVID-19, there are fewer reports of autopsies have been released which contain valuable information about immunopathology characteristic of COVID-19 (9). Due to multiple organ involvement in severe cases, increased autopsies around world countries from different involved organs can help to better understand the full aspects of the diseases such as COVID-19 (10).

To our knowledge this is the first report of histopathologic findings of postmortem COVID-19 biopsies from Iran which is one of the outbreak countries with more than 100000 confirmed cases.

Currently, the pathologic investigation has primarily focused on respiratory, hematopoietic, and immune systems, whereas morphologic data of liver and kidney injury are lacking.

In this study we aimed to investigate pathology of postmortem biopsy including the lungs, liver, and kidneys in two patients.

Method

In this study we reported two patients admitted to hospital with fever and respiratory symptoms. This study was approved by the Ethical Committee of Iran University of Medical Sciences. Clinical symptoms and past medical history were investigated. Laboratory tests and Computed tomography (CT) of the chest were performed.

After permission from the patients' families, postmortem needle core biopsies were performed on visceral organs including the lungs, liver, and kidneys shortly after death in a negative air isolation ward and complete protection. The procedures were performed with ultrasound guidance. Nasopharyngeal swabs for SARS-CoV-2 were positive (by rRT-PCR)

Case 1

The descent was a 57-year-old man without any past medical history visited in respiratory clinic with fever, malaise and cough last week. He had many sick contacts and nasopharyngeal swabs for SARS-CoV-2 were positive (by rRT-PCR). Computed tomography (CT) of the chest revealed mild infiltrations and he was not hypoxic on pulsoxymetry therefore he was treated as outpatient. The symptoms became deteriorated within a week and the patient admitted to intensive care unit due to difficulty of breath, high fever and diffuse ground glass opacity with some crazy paving and consolidation in chest CT scan (figure 1 a,b) (table 2). Laboratory tests at the time of admission is shown in (table 1). The patient was intubated because of severe hypoxemia. Different medications were performed by medical treatment team during admission such as antiviral drugs, Unfractionated heparin, IVIG, steroids, antibiotics and plasma perfusion. Actemra (tocilizumab) was also administered after nonreactive PPD skin test for tuberculosis due to elevated IL-6 level. The descent went into shock and cardiac arrest.

Lung biopsy

The findings of lung tissue histopathologic examination were similar to DAD (diffused alveolar damage) with focally fibromyxoid exudate. Interstitial and alveolar edema with foci of hyaline membranes and fibrinous exudate.

Intra-alveolar hemorrhage, moderately interstitial inflammation with composed of lymphocytes, plasma cells and neutrophils were seen. Focally necrosis and alveolar destruction were present. The other important findings are intravascular micro-thrombi and large multinucleated pneumocytes with focal presence of intranuclear inclusion like structure (may be due to viral cytopathic changes). Also desquamation of pneumocytes was noted. There was no evidence of mucus plugging with in airways. No granuloma or eosinophilic infiltrations were identified.

Histopathologic examination of Renal biopsy

Histopathologic findings mostly revealed mild acute tubulointerstitial nephritis (ATIN) with subtle attenuation of tubular epithelium, interstitial edema with mild lymphocytic infiltration. No granuloma and cytopathic effect were identified. Vascular damage and arteriosclerosis were not seen. Glomeruli were intact.

Case 2

A 83-year old man with past medical history of hypertension, diabetes mellitus , cerebrovascular accident (CVA) and end stage renal disease (ESRD) was referred to hospital with Emergency medical services (EMS) because of dyspnea, dry cough and fever for 2 days.

He had no history of recent travel or known contact with sick patient. At arrival he was hypoxic and febrile (temperature=39°C). Laboratory tests revealed lymphopenia and thrombocytopenia, elevated C-reactive protein (CRP), cardiac Troponin-I and D-Dimer (table 1).

Axial CT images of the lungs show extensive ground glass appearance in the lungs, mainly in the peripheral regions. Some crazy paving and consolidation is also present in addition to mild bilateral pleural effusion (figure 2 a,b) (table 2).

The decedent admitted to intensive care unit and suffered a cardiac arrest the next day.

Nasopharyngeal swabs for SARS-CoV-2 were reported as positive (by rRT-PCR)

Lung biopsy

Histopathologic findings of lung biopsy revealed diffuse alveolar damage (DAD) in early phase which was characterized by interstitial edema with focally fibrinous exudates and hyaline membranes. Intra-alveolar hemorrhage with mild interstitial inflammation consisted of lymphocytes and histiocytes and focal parenchymal necrosis were identified. Focal alveolar destruction was seen. Also large multinucleated pneumocytes without evidence of intranuclear or cytoplasmic inclusion was noted. There was no evidence of mucus plugging with in airways. No granuloma or eosinophilic infiltration were identified.

liver biopsy

The liver biopsy was consisted of mild lobular and portal inflammation dominated by lymphocytes. Moderate macrovesicular and mild microvesicular steatosis with diffuse distribution were noted. Moderate ballooning degeneration of hepatocytes with moderate bile pigment were identified. Hemorrhage and congestion as well as focal necrosis were also detected. Cytopathic effect and fibrosis were not seen. These findings indicated the injury could have been caused by either SARS-COV-2 infection or drug induced liver damage.

Discussion

To our knowledge this is the first autopsies from lungs, liver and kidneys in decedents with positive test for SARS-CoV-2 from Iran. In our study early phase of DAD was the main finding in microscopic examination of

the lungs, characterized by interstitial edema with fibrinous exudates and hyaline membranes. Our findings were similar to previous lung pathology studies from china in COVID-19 patients described DAD with edema, hyaline membranes, and inflammation, features characteristic of typical ARDS (9-12). There was no evidence of mucus plugging within airways or eosinophilic infiltration in lung autopsies.

The importance of this study was because some of previous reports suspected the pathology of lungs in covid-19 patients differ from diffuse alveolar damage (DAD) and hyaline membrane formation which are hallmarks of typical ARDS (13, 14).

The main pathology in both of our patients consisted of DAD with typical histopathologic findings (15).

Intravascular micro-thrombi were detected in one of our patients with high plasma levels of D-dimer and ferritin (2436 and 1220 ng/ml, respectively) despite anticoagulation therapy which support the hypothesis of pulmonary intravascular coagulopathy associated with elevated D-dimer and ferritin secondary to extensive pulmonary inflammation (16,17)

It is demonstrated that D-dimer is a significant independent biomarker of poor prognosis and values above 1000 ng/ml have been associated with fatal outcome of COVID-19 patients (18).

Increased ferritin and other inflammatory markers (CRP, interleukin-1, interleukin-6, and tumor necrosis factor) stimulate microvascular endothelial cell injury, intra-vascular coagulopathy and increased vessel permeability result in micro-thrombi formation and intra-alveolar hemorrhage (19).

In contrast to Margo and colleagues reported no viral cytopathic changes in lung tissues (20), Viral cytopathic changes followed by diffused alveolar damage and thrombotic microvascular injury was a remarkable finding of our study.

Due to prevalent organ involvement in COVID-19, pathologic investigations have essentially focused on respiratory and hematologic disorders, whereas limited data about kidney injury are released (21).

Clinically, the incidence of acute kidney injury (AKI) in COVID-19 varied from 0.9% to 29% in different centers. New onset proteinuria was also reported by several institutions (22).

One of our decedents suffered from new onset proteinuria, AKI and creatinine rise during admission. Renal autopsy revealed acute tubulointerstitial nephritis (ATIN) with subtle attenuation of tubular epithelium, interstitial edema and lymphocytic infiltration. Vascular damage or arteriosclerosis was not detected, whereas the decedent had no underlying disease. Glomeruli were intact.

Su H and colleagues examined 26 autopsies of patients with COVID-19 and revealed proximal acute tubule injury (ATI), occlusion of microvascular lumens mainly by erythrocytes with ensuing endothelial damage, as well as glomerular and vascular changes indicative of underlying diabetic or hypertensive disease (21). The researchers suspected SARS-CoV-2 virus might directly infect the renal tubular epithelium and podocytes, which was associated with AKI and proteinuria in patients with COVID-19 (21).

Liver biopsy revealed steatosis, lobular and portal inflammation. Hemorrhage and congestion as well as focal necrosis were also detected.

Conclusions

This study emphasis that diffuse alveolar damage and microvascular pulmonary thrombosis in SARS-CoV-2 patients is main pathologic finding of ARDS patients caused by either direct viral cytopathic effect or host immune and inflammatory reaction. These findings might describe severe hypoxemia in COVID-19 patients suffering ARDS.

Our data strongly indicates the role of appropriate oxygen support and anticoagulation therapy with strict monitoring.

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Figure legends

Figure 1. Case 1: Axial CT images show diffuse ground glass opacity with some crazy paving and consolidation (a,b). A small amount of lungs is spared. CT severity score is 38/40 according to the system proposed by Yang R, Li X, Liu H, Zhen Y, Zhang X, Xiong Q, Luo Y, Gao C, Zeng W. *Chest ct severity score: An imaging tool for assessing severe covid-19. Radiology: Cardiothoracic Imaging*. 2020 Mar 30;2(2): e200047.

Figure 2. Case 2: Axial CT images of the lungs show extensive ground glass appearance in the lungs, mainly in the peripheral regions (a). Some crazy paving and consolidation is also present in addition to mild bilateral pleural effusion (b). CT severity score is 24/40 according to the system proposed by Yang R, Li X, Liu H, Zhen Y, Zhang X, Xiong Q, Luo Y, Gao C, Zeng W. *Chest ct severity score: An imaging tool for assessing severe covid-19. Radiology: Cardiothoracic Imaging*. 2020 Mar 30;2(2):e200047.

Fig 3. Lungs and renal pathologic findings in case 1.

Pathological manifestation of lung tissue, Diffuse alveolar damage in acute phase (A)

Note hyaline membrane (arrow) (B,C)

Intranuclear inclusion-like structures (D)

Morphologically acute tubular necrosis on renal biopsy showing attenuation of tubular epithelium (E)

Fig 4. Pathologic findings of lung tissue (a,b) Diffuse alveolar damage

Pathologic findings of liver tissue. Hepatic steatosis (C)

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