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Autopsy Findings in Covid 19 Patients

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ABSTRACT

The Corona virus disease is the ongoing global pandemic caused by the virus, Severe Acute Respiratory Syndrome related coronavirus of genus Beta coronavirus (SARS-CoV-2). This deadly virus was identified first in China, in the city of Wuhan in December 2019, which lead to a lockdown in same city and other cities in Hubei province because they failed to contain the outbreak, and it spread rapidly like the forest fire to other parts of mainland of the continent China and around the world. The virus has caused a huge number of causalities and unknown manifestations in a lot of patients and the reason as to why so many patients died are the interest of the researchers all around. Post-mortem findings will provide us with information regarding important aspects of covid pathology and which cells are specifically targeted and infected. Very few studies and researches have been carried out which also make us short of data to work on but there were individual studies of various institute who carried out autopsies in order to find the exact causes of deaths. This review discusses the various clinical and pathologic and Immunohistological findings in patients who contracted covid 19 and suffered, although we still have very less data on the concerned topic. The virus attacked lungs primarily but has also affected other organs of the body. The casualties that occurred the most were due the lung involvement while the world also encountered some bizarre cases of involvement of cardiac tissue, hepatic and biliary system involvement, renal system and neurologic involvement. Although the latter have been more commonly associated with older population and co morbid patients.

Key words: Covid-19, Autopsy, SARS, Renal system

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INTRODUCTION

COVID 19 is the virus that has led to the pandemic of in the year 2019 all over the world. The virus has led to the feeling of apprehension and havoc all over the world due to its high contagiousness. There was a varied spectrum of symptoms seen among the patients of coronovirus. Some had mild cough and cold while to the other extreme of the spectrum of disease it presented with severe respiratory distress and post covid complications leading to a large number of demise all over the globe. There is currently no particular medicine or vaccine available to combat this fatal virus, necessitating research into the process through which the studies are made as to how the virus penetrates the host cell. According to data published in multiple journals, more than 9.65 million people have been infected with the virus, with 491,115 deaths confirmed as of June 27, 2020. Coronaviruses are encased, positive-stranded RNA viruses that are big and enveloped. On the surface, they feature spike-like projections formed of glycoproteins. The virus has an envelope from which the trimetric proteins protrude and are the primary mechanism that permits viral entry into the cell of the host. These trimeric S proteins are primary structural proteins [1,2]. SARS-CoV-2 recognises angiotensin-converting enzyme 2 (ACE2) receptors on human cells using the receptor-binding domain (RBD) of the spike glycoprotein, which starts the multistep process of viral entry into the host. This occurs by viral and host cell membrane when they undergo fusion through the conformational changes in the S protein occurring on large scale.(3)Autopsy findings are very important in gaining a better understanding of how this infection affects the human body, similar to how these findings are important to understand the dynamics of other infectious diseases. Further in the review article various studies have been reviewed and the findings from each study is summarized which would help us to know the extent of damage the virus has on the human body.

Autopsy findings

There are varied clinical manifestations of the illness, which begin from the patient being asymptomatic or symptomatic to the conditions that are specifically manifested by respiratory failure or severe respiratory distress requiring mechanical ventilation in the patients. In some patients who had severe disease have also undergone MODS which is multiorgan dysfunction. The clinical manifestations have been divided into the following three subdivisions based on the level of severity experienced in the patients:

1.Mild disease: characterized by uncomplicated and not so severe symptoms such as low grade fever, malaise, cough cold, nasal congestion. A majority of patient comprised of these.

2. Severe disease: characterized by increased rate of respiration, dyspnea and falling oxygen saturation. Patients present with acute respiratory distress, pneumonia and sepsis.

3. Critical: Patients who have had MODs, respiratory failure, cardiac injury etc.

The SARS COV 2 illness can pave way to severe pneumonia groups and even ards, which is the most frequent and familiar cause of death in patients with Coronavirus. A study was done on covid 19 patients who clinically correlated 41.8% patients with the development of Acute respiratory distress syndrome. While another study done higher figures in elderly and comorbid patients tend to develop more ARDS rather than young individuals and figures were as such that 16.9% elderly developed ARDS. On the contrary only 5.37% developed the same in young population [3]. They had this argument that older people were more commonly associated with a higher development of more severe disease and succumbed [4]. The study showed signs of inflammation in these patients such as increased levels of C reactive proteins and increased count of neutrophils. Also older and co morbid patients showed a higher frequency of ARDs which was an independent risk factor for death. There were instances when some patients visited hospital with the heart problems and were not even preceded by general symptoms like fever and cough. There only manifestation was cardiovascular involvement. The findings of cardiovascular involvement also showed how Heart injury is also one of the key causes of deaths in sufferers of COVID-19 virus. Another study done revealed 40% of the patients died due the cardiovascular co morbidities such as they had circulatory failure due to cardiac tissue injuries. This study also showed that the incidence of heart tissue injury was more in older patients in comparison to the young patients aged less than 60 years. There were varied signs and symptoms for which patients presented to the hospital with corona virus illness. The disease obviously showed milder symptoms in young patients while the old patients specifically with age more than 60 years were presenting with severe infection and were harder to treat.

Radiological correlation of the disease with the findings in patients

Radiological and pathological studies revealed more apparent fibrosis and alveolar structural damage in sub pleural locations. The lesions present in the areas, marginal in lungs were more serious, according to radiological and gross exams. There were some discrepancies in our histological findings between the subplueral and central areas. Proliferation of fibrous tissue in the alveolar septa and alveolar disintegration were particularly common towards the periphery. The alveolar structure was essentially intact in the core portion, with minimal localised fibrosis within alveolar septa. Within the alveolar space, serous and macrophage exudation were visible. This could be due to variations in time and space, as well as the intensity of the lesions. Lesions in the periphery of the lobe tended to form earlier and remain longer, making them more severe than those in the centre. This was further supported by CT findings indicating Ground glass opacities and fibrosis frequently started in the subpleural space. As the condition worsened, further opacities of a certain kind of appeared.

Different Ground glass opacities are the foundational and basic sign on CT imaging of COVID-19 pneumonia, in addition to the unique distribution manner. There was presence of exudation of the implicated inflammatory cells such as, lymphocytes and other substances such as protein and fibrin all of them formed a membrane substance in the alveolar space. This exudative membrane formation was caused by pathogens invading the bronchioles and alveolar epithelium and replicating in there. This produces dyspnea because blood-oxygen exchange is hampered [5]. The most common CT findings were Ground glass opacities which seem to look like crushes glass appearance in lungs with consolidation and may be associated with interlobular septal thickening, which were commonly referred to as "paving stone signals," as well as lungs appearing pale known as white lungs which indicated not so good outcome. Proliferation of fibrous tissue was observed in the alveolar and interlobular septas as a result of the pathological findings. Consolidation occurs after proliferation of fibroblasts, type II alveolar epithelial hyperplasia, adenoid alveolar development, and filled alveoli with organized exudation.

Hyaline membranes were frequently seen in extremely ill and terminally ill patients in some studies that were done. Another study indicated that COVID-19 was present at the time of surgery in two sufferers who had lung lobectomies for malignancy. Hyaline membranes were not visible in the asymptomatic and early stages. If serious ground glass opacities or even classical consolidation and interlobular septal thickening were seen a s result, these findings are based on exudation present extensively across the lungs and in case hyaline membrane formation, and lung fibrosis, were the presentation soon after symptoms began to appear in the patient, all of this usually indicates a potential risk of

poor prognosis in CT and clinical outcomes in the short term. Radiological studies, particularly high-resolution CT scans, are extremely useful in identifying people who are at danger of becoming critically sick and will benefit from intensive care treatment. However, distinguishing fibrosis- or organized exudation-based consolidation from CT images remains difficult.

Findings that have been reported in deceased patients

After carrying out the immunostaining of the bronchoalveolar fluid which was obtained from the lungs of patients that suffered from the severe covid 19 virus disease, it showed a large quantity of chemokine's which were released by the macrophages. The surface of the macrophages in the lymph nodes ,subscapular and marginal zone of spleen expressed the ACE2.It was shown that these macrophages contained the nucleoprotein of SARS coV 2 virus although after the analysis using RNA sequencing the expression of the ACE2 receptors could not be established and thus the causative reason and association of virus and ACE2 receptors are yet to be proven [6].

Another study on a patient who was suffering from the severe respiratory symptoms since 14 days and succumbed to the cardiac arrest while an episode of respiratory insufficiency. this study included taking biopsies from the various organs such as heart, lung, brain and liver.The biopsy of the lung showed following findings suggestive of the covid virus infection such as diffuse alveolar damage was seen in lungs with edema and infiltrates of the lymphocytes and pneumocytes showed multinucleated syncytial cells, very suggestive of the virus [7].

There was another study done by Zhang et al on a 72 year old patient whos lung biopsies remained the same and showed same results as the studies done earlier in other patients in different institutes all over the world.

Post-mortem findings of heart in COVID-19 patients

Coronavirus is associated with cardiomyopathy and myocarditis, although other viruses are also known to cause them. All the patients who were infected showed various findings ranging from giant cell/granulomatous cardiac inflammation and infiltration with lymphocytes and eosinophil's. This granulomatous inflammation has led to infectious dilated cardiomyopathy in some patients [6]. COVID-19 caused cardiac damage that resulted in mortality in roughly 7% of patients and contributed to death in another 33%. Pericardial effusion was discovered during an autopsy of a COVID-19 patient. The deceased patient's macroscopic findings were described as "fish skin like, crimson or grey in colour" and on microscope revealed diffuse inflammatory infiltrates which consisted of lymphocytes and macrophages with significant number of eosinophil's present at the site of inflammation thus confirming the inflammation. The results revealed main interstitial inflammation, which was linked to several foci of necrosis the contractile cells of the hearts muscles myocytes. This finding was consistent with both the right and left ventricles in the absence of any vessel wall inflammation or fibrinoid necrosis, and it was not angiocentric, granulomatous, or linked with vasculitis. Cardiomegaly and the dilatation of the right and left ventricles were the gross findings in covid 19 patients.

Hematology, renal and other findings in COVID-19 patients

In a Brazilian research, 80 percent of COVID-19 patients had fibrin thrombi in their alveolar arterioles. This is a sign of a state where coagulation in the bodies increases in critically ill patients, which can result in a ventilation-perfusion mismatch in the lungs and a peripheral ischemia event. increased in coagulation in the bodies indicated towards the poor prognosis of the patient as hypercoagulability will further lead to the formation of thrombus and this thrombus broke to form small emboli's that went into the micro circulation and into various organs such as lungs, liver, heart, brain and upper and lower extremities. These emboli's thus then activated the coagulation pathway in the body leading to Disseminated intravascular coagulation. This process of inflammation was mediated by the inflammatory cytokines which were implicated in the covid 19 disease. The findings in the brain too correlate with the hypercoagualtion occurring in the body. According to a study on a deceased patient of covid 19 viruses, after his nueropathological examination was done, it showed hemorrhages in the white matter all over the cerebral hemispheres. Microscopically it also showed the presence of macrophages and other inflammatory cells. The macrophages occurred in clusters in the subcortical region. There was also perivascular acute disseminated encephalomyelitis like appearance and there were areas of focal necrosis. The examination also revealed injury to axons.

Autopsy reviews of 10 sufferers have been taken from Hospital Graz II located in Austria, that's the second-biggest public and educational health center in Austria, confirmed the consequences as followed: thrombosis of the small-sized and mid-sized pulmonary artery at specific ranges in all of the sufferers, bronchopneumonia in six sufferers and hepatic congestion in 8 sufferers. The different findings in the liver had been additionally stated as follows

- ✓ Lymphocytic infiltrates.
- ✓ Hepatic steatosis.
- ✓ Portal fibrosis.
- ✓ Proliferation of the ducts.
- ✓ Lobular cholestasis, and
- ✓ Liver cell necrosis, associated with central vein thrombosis.

Some other findings revealed focal pancreatitis, adrenocortical hyperplasia, depletion of lymphocytes

in the spleen and lymph nodes and renal proximal tubular injuries. There have been findings that show kidney involvement directly by the particles of virus that were very similar to SARS-CoV-2 morphologically. A light microscopy was done which showed tubular isometric vacuolization which were similar to double membrane vesicles containing vacuoles found on electron microscopy. The University Medical Center Hamburg-Eppendorf also carried out post mortem on 12 sufferers which showed pulmonary embolism was the direct reason of demise in twelve sufferers, which were originated from the deep veins of the lower extremities also known as deep venous thrombosis. The post-mortem found out deep vein thrombosis in seven out of 12 sufferers, wherein thromboembolism had no longer been suspected on the time of demise. Disseminated intravascular coagulation can be blamed for renal failure as it had led to the micro thrombi formation, damaging the kidneys.

After the various studies showed how microthrombis and emboli's caused damaged to the other organs in the body a major culprit in this process was the dysfunction in the hematological system which can be blamed to the coagulopathy induced by the virus. The hematological dysfunction led to the lymphocyte damage. There was also depletion of the white pulp of spleen and further leading to the decreased white blood cells counts paving way to numerous infections and can lead to cardiovascular diseases too.

The extra pulmonary findings such as septicemia and septic shock, myocarditis dermatitis, myositis and kidney related problems were seen to be associated in patients already immunocompromised or having preexisting comorbid condition such diabetes and Hyperion.

CONCLUSION

Among all the findings seen in various systems the most relevant autopsy findings were the findings in the lungs if the sufferers which included diffuse alveolar damage of lungs and presence of inflammatory exudates and cytokines leading to pulmonary edema and hyaline membrane disease in almost all cases. Other pulmonary findings, including acute respiratory distress syndrome and tissue from the lungs, were usually positive for the 2019 viral antigen. The other significant extra pulmonary findings require intensive research and the data available over them is too less to associate any specific finding to the cause therefore autopsy plays a very is important role in finding a lot more manifestations that covid 19 causes on the human body. The hypercoagulable state and use of anticoagulants is yet to be studied more as to how effective it is. Out of all the articles that were reviewed, the lung findings remain unchanged while the extra pulmonary findings of various organs showed varied results, the finding in the brain showed hemorrhages in the cerebral hemispheres white matter and foci of necrosis. In liver, wide range of macroscopic and microscopic changes were seen such as lymphocytic infiltrate. Steatosis and liver cell failure and necrosis. In heart. Dilatation of ventricles and cardiomegaly can be seen. Coagulopathy and activation of coagulation pathways was initiated by viral particles leading to dysfunction in the hematological system further leading to DIC and death. Out of all pulmonary changes remain consistent with all the deaths due to the virus.

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