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REVIEW OF CARDIOPULMONARY AUTOPSY FINDINGS IN DECEASED COVID-19 POSITIVE PATIENTS IN A TERTIARY CARE CENTER IN CENTRAL INDIA

Pathology

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ABSTRACT

COVID-19 is global pandemic caused by the SARS-CoV-2 virus. COVID-19 is a systemic multiorgan disorder with major involvement of the lungs and heart leading to Interstitial Pneumonia, Diffuse Alveolar Damage (DAD) and Acute Respiratory Distress Syndrome (ARDS). An important mechanism responsible for the widespread COVID-associated mortality is presumed to be the ineffective immune responses to the SARS-CoV-2 virus along with an associated thrombotic microangiopathy that ultimately leads to multiorgan failure and death. Even COVID-19 survivors with preexisting comorbidities; especially the elderly, run a risk of secondary neurologic and cardiopulmonary complications and might sometimes succumb to sudden death. Autopsy findings are crucial to gaining a better understanding of the pathobiology of this "novel" disease as well as analyzing its long-term effects on target organs. In India, due to the prohibitive regulations regarding COVID autopsies; very little data is available on autopsy histopathology of patients dying of COVID-19; as well as those recovering from the disease, only to pass away during the recovery period. The present study aims to document the cardiopulmonary abnormalities found in autopsies of COVID-positive patients conducted at our institution while simultaneously conducting a review of the available international literature on the related topic. This will be particularly of interest for clinicians treating COVID-19 in Central India, as; of now, no similar studies have been reported from this region.

KEYWORDS

COVID-19, Pneumonia, DAD, ARDS, Myocarditis, Microangiopathy, Autopsy, Histopathology

INTRODUCTION:

The novel corona virus SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) infection has affected almost all the nations of the world. The World Health Organization had declared it a pandemic on 11th March 2020. This is a disease with an increasing number of severely ill patients which puts a burden on our healthcare infrastructure.[1]

COVID-19 has become a challenge for all healthcare professionals because this is a 'novel' strain leading to a 'novel' disease about which not much has been studied and not much is known. Available literature indicates that COVID-19 is a systemic disease with major involvement of the lungs and heart. Autopsy findings are crucial to gaining a better understanding of how infectious diseases affect the human body. Thus, for studying the pathobiology of this new infection, postmortem examination is a valuable tool.[1,2,3]

SARS-CoV-2 is a respiratory virus. Autopsies from patients with COVID-19 confirm that majority of severely affected patients have significant pulmonary pathology. COVID-19 produces an acute interstitial pneumonia, usually with a prominent diffuse alveolar damage (DAD) component. However, an important additional mechanism that contributes to death is thrombotic microangiopathy. Mediators released during cytokine storm overlap with those of thrombotic microangiopathy, suggesting that ineffective immune responses to SARS-CoV-2, severe interstitial pneumonia, ARDS, multiorgan failure and life-threatening microangiopathy are closely related to each other. [1,2,12]

As more data emerges from the COVID-19 pandemic, it is gradually becoming clear that there is an important cardiovascular component to this disease as well. The heart frequently shows acute cardiomyocyte injury and, in some cases, pericarditis and/or myocarditis. Patients with fatal COVID-19 frequently are obese and have pre-existing cardiac disease, hypertension and/or diabetes mellitus.[3]

Numerous studies have shown that COVID-19 survivors with preexisting comorbidities; especially those who are of older age, have substantial physical as well as psychological disabilities and also run a risk of secondary neurologic and cardiopulmonary complications.[4,5] Sometimes, sudden death may be encountered in such patients outside the hospital setup. Death may also occur unexpectedly in apparently previous healthy individuals after a brief period of trivial flu-like symptoms. In such doubtful cases, the forensic pathologist can help in defining the cause of death.[6]

However, not much data is available on autopsies conducted on those patients who seem to have apparently recovered from COVID 19, yet inexplicably pass away during the post recovery period. In our country, this conundrum is further aggravated by an administrative ruling that prohibits autopsies in COVID positive cases barring a few special circumstances.[7]

As rightly emphasized by Balachanda et al., the need of the hour is to conduct more longitudinal studies to assess the health status of the COVID-19 recovered patients. Follow-up survey of COVID-19 recovered patients will be helpful to evaluate any long-term changes in the other organs inhuman systems.[5]

MATERIALS AND METHODS:

STUDY DESIGN: Bodies of three COVID-19 positive patients was received at the Forensic Medicine and Toxicology Department, CIMS, Bilaspur. Due to the medicolegal implications involved, autopsies were conducted on these patients in accordance with MOH&FW regulations[7] and with the consent of the decedent's kin. As our institution is a tertiary care non-COVID hospital, the only patients referred for treatment to our institute are those who had previously contracted and subsequently recovered from COVID-19. Thus, the autopsies were conducted to rule out post-COVID complications as the possible cause of death. Subsequently the heart and lungs of the autopsied patients were submitted to the Forensic Histopathology Section, Department of Pathology, CIMS, Bilaspur for histological examination.

INCLUSION AND EXCLUSION CRITERIA:

Due to the paucity of the number of cases no inclusion and exclusion criteria were set.

DATA COLLECTION:

Relevant information was collected regarding the age, sex, nature and duration of presenting complaints for which the patients sought medical intervention. Detailed medical history including history of comorbidities known to predispose to COVID-19 and treatment received prior to death was obtained.

GROSS EXAMINATION:

The received viscera were weighed, measured and detailed descriptions of grossly appreciable pathological findings were noted.

MICROSCOPIC EXAMINATION:

Tissue sections at 6µ were cut and slides prepared, which were

subsequently stained with H&E stain and examined under the microscope.

OBSERVATION:

Table 1: Clinical Presentation

Case No.	Age	Sex	Known Comorbidities	COVID Disease Category	Symptom-free interval after Covid recovery	Post-COVID Symptoms	Duration from Hospitalization until Death (in days)
1.	70	M	HT, DMII	ILI	1 month	Severe Chest Pain, Collapse	0 (brought dead)
2.	90	F	HT	Mild ILI	14 days	Loss of Consciousness	1
3.	75	M	COPD with PAH	SARI	-	Severe Breathlessness, Constriction feeling in chest	5

Table 2: Autopsy Findings in Heart- Gross

Case No.	Weight in gms.	Dimensions in cms.	External Surface	Cut Surface
1.	492	11x11x6	Heart enlarged in size, bulky Vertical rupture in Anterolateral LV wall (8x2 cm) Hemopericardium with approx. 100ml blood in pericardial cavity	RV- 0.8CM LV- 1.4 CM IVS- 1.6 CM RCA- thickened LCA-thickened, PM clot +
2.	688	14.5x10.5x5	Heart enlarged in size, flabby in consistency	All chambers dilated RV-0.5 CM LV-1 CM IVS-1.3 CM RCA & LCA- grossly unremarkable
3.	469	10x9.6x5.5	Heart slightly enlarged. Thick epicardial fat pad. Anterior descending artery appears thickened and prominent	RV- 0.8 L.V-1.3 IVS-1.5 RCA- thickened, PM clot + LCA-thickened, cord-like, clot +

Table 3: Autopsy Findings in Heart- Histopathology

Case No.	Microscopic Findings	Diagnosis
1.	Extensive areas of ischemic cardiomyocyte necrosis. Marked myxoid degeneration in necrotic areas in IVS and LV wall, especially on both sides of the ventricular tear. Diffuse infiltration of lymphocytes in the interstitium. Lipofuscin pigments and macrophages seen at places. Epicarditis noted in sections from RV. Microthrombi present in arterioles near infarcted areas. Other small caliber blood vessels show congestion. Both RCA and LCA show fibroatheroma with narrowing of lumen.	Cardiac Tamponade following rupture of Ventricular Aneurysm (complications of CAD & MI)
2.	Elongated cardiomyocytes with increased nuclear size. Focal areas of ischemic cardiomyocyte necrosis. Interstitial fibrosis surrounding individual or small groups of necrotic cardiomyocytes. Mild fatty infiltration in interstitium. Mild inflammatory infiltration in the interstitium. Lipofuscin pigments seen occasionally. Myocardial blood vessels show medial hypertrophy with diffuse intimal hyperplasia. RCA & LCA show medial hypertrophy and irregular intimal hyperplasia.	Dilated Cardiomyopathy with Age-related Coronary Vascular Changes
3.	Focal areas of ischemic cardiomyocyte necrosis. Interstitial fibrosis surrounding individual or small groups of necrotic cardiomyocytes. Mild inflammatory infiltration in the interstitium. Thick epicardial fat pad. Epicardial and myocardial blood vessels show medial hypertrophy. RCA - early atheroma formation, severe irregular intimal hyperplasia, focal areas of foam cell and cholesterol crystal deposition in intima. LCA- diffuse intimal hyperplasia.	CAD with Chronic IHD

Table 4: Autopsy Findings in Lung- Gross

Case No.	Weight in gms	Dimensions in cms	External Surface	Cut Surface
1.	820 gm only rt. Lung received	13x12x5	Part of lower lobe not included (submitted for other forensic inv.) Lung appears heavy, external surface mottled with patchy, dark, brownish areas.	Loss of sponginess, decreased air entry, mottled blackish appearance
2.	350g approx.	Bits of lung tissue together measuring 4x4x3cm.	Both lungs fibrotic and adherent to the chest wall; could only be removed in bits and pieces	Loss of sponginess, greyish white areas visible. Pleura thickened.
3.	Rt. Lung-980 gm Lt. Lung-820 gm	Rt. Lung-12x7x6 Lt. Lung-9x6x5	Part of lower lobe not included (submitted for other forensic inv.) Rt. Lung: appears heavy, external surface greyish, hemorrhagic Lt. Lung: external surface mottled with multiple blackish spots	Rt. Lung: solid, liver-like consistency in focal areas; loss of sponginess, decreased air entry. C/S appears greyish brown to brownish-black Lt. Lung: Loss of sponginess, decreased air entry, mottled blackish appearance

Table 5: Autopsy Findings in Lung- Histopathology

Case No.	Microscopic Findings	Diagnosis
1.	Disruption of alveolar lining. Compression of alveolar spaces. Emphysematous dilatation of unaffected alveoli. Widening of interalveolar septae. Increased no. of Type II pneumocytes. Atypical	DAD, Organizing / Proliferating Phase

	pneumocytes & pneumocytes with viral inclusion bodies seen. Congestion of septal blood vessels. Focal areas of septal hemorrhage and heart failure cells. Collagen and elastin deposition in perivascular and peribronchial location. Devitalization of bronchial epithelium. Numerous coal macules.	
2.	Marked collagen fibrosis and elastofibrosis Destruction of alveolar architecture Few cystic alveolar spaces surrounded by thick fibro-collagenous bands : honeycombing Mild to moderate infiltration by inflammatory cells Pleural thickened and fibrotic.	Pleurisy with Interstitial Lung Disease
3.	Disruption of alveolar lining. Necrotic and atypical pneumocytes. Atypical pneumocytes and pneumocytes with viral inclusions seen. Most alveolar spaces compressed; few show emphysematous dilatation. Presence of hyaline membranes. Intra-alveolar hemorrhage. Marked alveolar and interstitial edema. Patchy areas of consolidation. Widening of lung interstitium with intra-septal hemorrhage, chronic inflammatory infiltrates and hemosiderin laden macrophages. Presence of microthrombi and megakaryocytes in alveolar capillaries. Medium sized vessels show medial thickening. Massive congestion of bronchial blood vessels.	DAD, exudative phase with Pulmonary Edema.

DISCUSSION:

Autopsy studies on COVID-19 have established that it is a multisystem disorder with a major, and often fatal, cardiopulmonary component; the underlying pathogenic mechanism appears to be a life-threatening microangiopathy. [1,2]

Age, Sex & Clinical Presentation: (Table 1).

Numerous studies have shown that COVID-19 survivors with preexisting comorbidities; especially those who are of older age, and having pre-existing cardiac disease, hypertension and/or diabetes mellitus run a high risk of secondary neurologic and cardiopulmonary complications.[2,3,4,5] In accordance, all the 3 deceased in our study were found to be older than 70 years and suffered from co-morbidities known to predispose to COVID-19 (Case No.1- HT & DMII; Case No. 2-HT; Case No. 3- COPD). [1,2,3,4]

Clinically, the first two cases were categorized as Influenza Like Illness (ILI) and the third as Severe Acute Respiratory Illness (SARI), as per WHO Influenza Surveillance Case Definitions.[8]

In the first case, the 70y/M patient had recovered from COVID-19 infection. After 1 month of symptom free interval, he suddenly complained of severe chest pain and collapsed; and was declared to have been 'brought dead on arrival'.

In the second case, the 90y/F patient, who had been treated and discharged following the 14-day quarantine period for mild ILI, suddenly lost consciousness and fell down. She was admitted at our institute in a comatose state, from which she did not recover until her death the following day.

The third case was that of a 75y/M admitted with SARI-like symptoms of fever, severe breathlessness and marked reduction of SPO2. The patient continued to deteriorate in spite of all efforts and expired after 5 days of hospitalization. Even though he initially tested COVID-negative, the result of a repeat RT-PCR test (received after the patient's death) confirmed him to be COVID-positive.

Gross Examination:

Heart: (Table 2). The normal average cardiac weight adjusted for age and sex is 345.9 g for men and 285.1 g for women at 61-70 years.[9] Autopsied hearts of COVID patients have shown evidence of cardiomegaly and an increase in heart weight, ranging from 340 g to 1010 g, especially in patients with history of cardiovascular disease.[3,10,11,12,13] Valvular heart disease has the greatest impact on heart weight, followed by old myocardial infarction, coronary atherosclerosis, and hypertension.[10]

In our study however, the heaviest weighing heart was found in Dilated Cardiomyopathy as seen in Case No. 2 (688 g); followed by Coronary Atherosclerosis and Myocardial Infarction as seen in Case No.1 (492 g). The patient was a known diabetic and hypertensive. Case No. 3, having Coronary Atherosclerosis with Chronic Ischemic Heart Disease recorded a heart weight of 469 g. In all the three cases studied by us, cardiomegaly and increase in heart weight was found in accordance to these findings.

Older COVID patients with preexisting comorbidities like hypertension, coronary artery disease, heart failure, and diabetes are prone to develop a significantly higher risk of sustaining myocardial injury and higher short-term mortality rate.[15,16] This could be corroborated in both Case No. 1 & 3.

Case No. 1 was a known diabetic and hypertensive, who, one month after recovering from COVID, succumbed to a massive myocardial infarct. A rupture in the anterolateral LV wall was revealed upon autopsy, along with well as presence of calcified fibroatheromas in both coronary arteries.[2,12] In Case No. 3, autopsy examination of the heart revealed a thick epicardial fat pad as well as a developing atheroma in the LCA.[2,17]

Coronavirus may be associated with infectious dilated cardiomyopathy. As observed in Case No. 2 of our study, such cases are grossly observable as cardiomegaly with right and left ventricular dilatation with thinning of ventricular walls.[12,13,18,19]

Lungs: (Table 3). Normal postmortem weights of right & left lungs are 608.32 g & 505.86 g respectively for men and 481.68 g & 410.90 g respectively for women, reaching peak weights of 720.70g for right and 573.11g for left lung in the 61-70yr age group.[20] However, in most autopsy lung studies of COVID 19 decedents, the combined weight of was found to be >1300 g (average upper limit of normal)s.[21] In our study, the individual and combined lung weights in Case No. 1 & 3 were found to be well above the upper limits of normal levels adjusted for age and sex and were comparable to the findings recorded by other authors.[2,21] No conclusive opinion could be derived in Case No. 2 due to the paucity of the sample received.

Gross examination of specimen in Case No. 1 showed heavy, congested and edematous lung[22,23,24,25] with patchy, dark, brownish mottling of external surface with cut surface showing loss of sponginess, decreased air entry and mottled brownish to blackish hemorrhagic appearance[26,27,28,29,30]. Similar findings were also seen in the lung specimens in Case No. 3 with the right lung additionally showing areas of patchy consolidation[14,31], while the left lung showed frank areas of parenchymal hemorrhage.[2,22,27,28,30] Even though pleuritis and pleurisy have been reported in the setting of COVID 19[19,32], we were unable to conclusively attribute similar findings in Case No. 2 to COVID as other preexisting pathologies could not be ruled out due to lack of sufficient clinical information and tissue specimen.

Microscopic Examination:

Heart: (Table 4). Patients with cardiovascular disease have the highest Case Fatality Rate (10.5%) among those COVID patients with medical comorbidities.[33] However autopsy histopathology studies show a wide variety of abnormalities ranging from myocyte hypertrophy to isolated/focal cardiomyocyte necrosis[3,11,34,35] to full blown myocardial infarction.[2,36]

In accordance with the former, we found evidence of individual and small groups of necrotic cardiomyocytes surrounded by interstitial fibrosis in Case No. 2 & 3. With regard to Case No. 1, our findings correlated most closely with the findings of Elsoukkary S.S. et al[2] where we found extensive areas of infarction with myxoid degeneration and rupture of the ventricular wall. (Figure 1). Fibroatheromas causing narrowing of lumen were found in RCA in Case No. 3 and both coronary arteries in Case No.1, which was again in keeping with the findings of Elsoukkary S.S. et al[2]. The elongated cardiomyocytes seen in Case No. 2 could be due to the shear stress on the dilated myocardium.

There is wide variance in the references regarding the degree of and nature of inflammatory infiltrates[13,18]; with Fox etal[11], Bryce et al[31], and Tian et al[35] reporting insignificant or mild inflammatory infiltration, while others have found evidence of myocarditis[2,3,13,19,37,38], epicarditis[31,38] and pericarditis[3,40] in their studies. All the three cases in

our study showed mild interstitial lymphocytic inflammatory infiltrates. Additionally, Case No.1 also showed interstitial macrophage infiltrates as well as evidence of prominent epicarditis, similar to the findings of Eketunde et al[13] and Basso et al.[40]

Microthrombi present in arterioles near infarcted areas in Case No. 1 (Figure 1) is also in accordance to the findings of Bryce et al[31], and Duarte-Neto et al[37].

However, none of the three cases in our study showed any evidence of naked megakaryocytes in myocardial capillaries as reported by Tombolini et al[6] or endothelial atypia/endothelitis as reported by Fox et al[11].

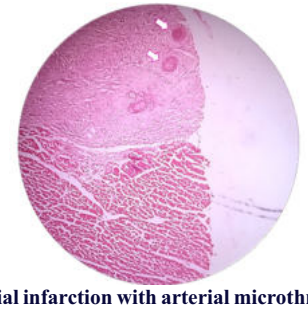

Fig. 1. Myocardial infarction with arterial microthrombi (arrows) in infarcted areas

Lungs: (Table 5).

The hallmark pulmonary pathology in COVD 19 is an Acute Respiratory Distress Syndrome (ARDS) manifested histologically as Diffuse Alveolar Damage (DAD).[1-6,10-14,19-32,35-44] ARDS/ DAD is histologically characterized by 3 phases: Exudative, Proliferative/ Organizing, And Fibrotic.[45]

The Exudative Phase of ARDS is characterized by the destruction of Type 1 alveolar cells and the capillary endothelial cells with accumulation of protein-rich edema fluid and cellular debris in the alveolar spaces and collapse of alveolar sacs (Figure 2a, 2b). The most characteristic feature is the presence of hyaline membranes lining the alveolar ducts (Figure 2c). Additional features are viral cytopathic effects including viral inclusion bodies; septal widening due to congestion and edema; interstitial and intra-alveolar hemorrhage along with the presence of microthrombi (Figure 3) and megakaryocytes in pulmonary capillaries. All the aforementioned findings were seen in Case No. 3.[3,6,13,19,23-26,28-32,36-44]

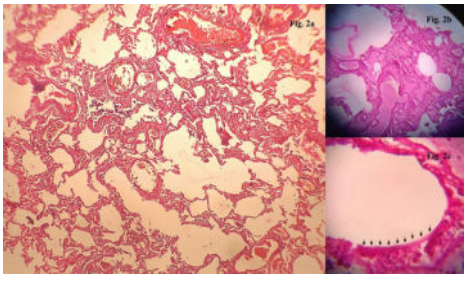

Fig. 2. Diffuse Alveolar Damage: Exudative Phase.

a. collapse of alveolar sacs, cellular debris in the alveolar spaces, destruction of Type 1 alveolar cells congestion & of blood vessels b. accumulation of protein-rich edema fluid in alveolar sacs c. hyaline membrane (arrows)

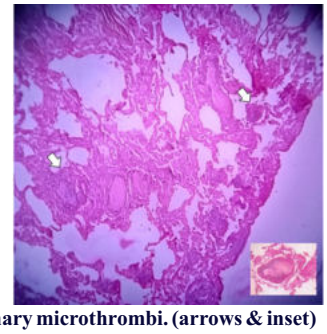

Fig. 3. Pulmonary microthrombi. (arrows & inset)

The Proliferative / Organizing Phase of ARDS is characterized by the onset of repair and resolution of the pathophysiological changes. The prominent microscopic features of this stage are interstitial and intra-alveolar proliferation of fibroblasts & myofibroblasts (Figure 4a, 4b); organizing or remnants of hyaline membrane; reactive hyperplasia of Type II pneumocytes (Figure 4c); interstitial lymphocytic infiltrates & evidence of endothelial injury along with thromboembolism in arteries / arterioles. In COVID related ARDS, many authors have reported additional findings of highly atypical Type II pneumocytes, Type II pneumocytes containing viral inclusions bodies as well as syncytial fusion of the pneumocytes (Figure 4c).[2,6,19,25,27,35,38,42] The histomorphology of the lung specimen of Case No. 1 in our study showed most of the aforementioned features (except for endothelial abnormalities). Clinicopathologically, the closest correlation in our case could be seen with the case reported by Zhang et al.[44]

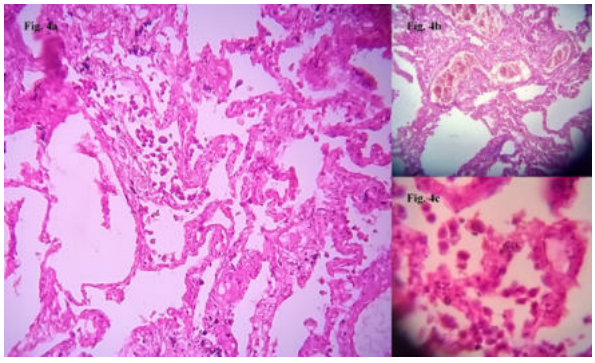

Fig. 4. Diffuse Alveolar Damage: Proliferative/Organizing Phase.

a. reactive hyperplasia of Type II pneumocytes b. interstitial and intra-alveolar proliferation of fibroblasts c. syncytial fusion of the pneumocytes with viral inclusions bodies (inside white circle)

The Fibrotic Phase of ARDS was reported only in a few cases of COVID-related lung disease.[12,29,36,38] In this phase, the inflammatory exudates are replaced by extensive alveolar and interstitial fibrosis. The remaining alveolar spaces are disorganized and surrounded by thick fibro-collagenous bands giving rise to a microscopic honeycomb-like change.[45] Reactive squamous[2,45] and even osseous[38] metaplasia may be seen in the residual tissue. Intimal fibrosis of pulmonary vessels may lead to progressive vascular occlusion and pulmonary hypertension.[45] In our study, even though the features in Case No. 2 closely resembled a majority of these findings, we could not conclusively attribute the findings to COVID due to our inability to rule out preexisting pathologies in the absence of sufficient clinical information and sample tissue.

Some cases of DAD in the autopsied specimens also showed evidence of superimposed pneumonia, a finding which was also reflected in Case No. 3 of our study.[3,24,27,29,31,32,4245]

REVIEW OF LITERATURE:

When a new or re-emergent pathogen, such as SARS-CoV-2, causes a major outbreak, rapid access to pertinent research findings is crucial for planning strategies and decision making.[46] As the COVID 19 pandemic spread rapidly, causing widespread major morbidity and mortality; it became crystal clear to forensic pathologists and allied physicians that autopsy of deceased victims of the disease was of paramount importance for gaining knowledge of its pathogenesis and pathophysiology.[3] Therefore, a detailed review of the postmortem gross and histopathological findings in lungs and heart, the organs most conspicuously affected by the SARS-CoV-2 virus, will help highlight the pathognomonic signs of COVID 19 disease.[1,13]

Autopsies performed on COVID-19 patients may be broadly divided into two groups: minimally invasive autopsies and complete autopsies.[1]

The earliest postmortem studies were minimally invasive autopsies conducted in the form of ultrasound-based minimally invasive autopsies (Dolhnikoff et al.)[42]; postmortem transthoracic needle biopsies of the lungs (Zhang et al.)[44]; core biopsy samplings of lung, heart, and liver (Xu et al.)[47] etc. Li et al. analyzed the three-dimensional histology reconstruction obtained from lung tissue samples of patients

who died because of COVID-19 and were able to document viral cytopathic changes in pneumocytes as well as emphasize the presence of megakaryocytes & fibrin aggregates in pulmonary capillaries.[48]

Subsequent reports of complete autopsies performed by Elsoukkary et al.[2], Buja et al.[3], Tombolini et al.[6], Fox et al.[12] etc. helped to grasp a better understanding of the pathobiology of this "novel" disorder.

The hallmark pulmonary pathology in COVD 19 is an Acute Respiratory Distress Syndrome (ARDS) / Diffuse Alveolar Damage (DAD).[1-6] The features are similar to the pulmonary damage observed in the previous Coronavirus mediated epidemics SARS (Severe Acute Respiratory Syndrome) and MERS (Middle Eastern Respiratory Syndrome).[49,50] However, unlike the SARS and MERS viruses, the SARS-CoV-2 virus disproportionately affects older patients with comorbidities such as hypertension, diabetes, obesity, and cardiovascular disease.[51]

Grossly; even though the most conspicuous morphological abnormalities were reported in the lungs, Elsoukkary et al.[2], Buja et al[3], Fox et al[12]., Fitzek et al.[23] documented evidence of cardiomegaly and increase of heart weights above the normal range for age and sex[9] in COVID 19 decedents. As expected, most autopsy lung studies found the combined weight of >1300 g, with Borczuk et al. recording individual lung weights as heavy as 1100g.[1,2,21]

Histologically, the most frequent pathological finding is both exudative and proliferative DAD as documented by Fox et al.[12] and others.[2,24,27,29] Though infrequently, late-stage DAD has been reported in the studies of Fox et al.[12], Remmelink et al.[36], Schaller et al.[38] and Zhang et al.[44] Of particular interest is the report of reactive squamous and osseous metaplasia in a case of Fibrotic DAD studied by Schaller et al.[38]

Konopka et al.[41] found heavy lung with mucus within the airways in an asthmatic patient who died of COVID 19 infection and documented chronic asthmatic alterations of the airways in addition to features of acute exudative DAD. Organizing pneumonia was found by Elsoukkary et al.[2] and Buja et al.[3]; while Menter et al.[24], Bradley et al.[27], Edler et al. [29] and others[29,31,32,42] were able to recognize superimposed bacterial pneumonia upon histological examination. Another significant finding reported by most authors was viral cytopathic effect on the pneumocytes; with Tombolini et al.[6] documenting marked cytological atypia, syncytial aggregate formation and Cowdry Type A viral inclusion bodies in the pneumocytes.

Conversely, however, Lacy et al.[28] and Aguiar et al.[30] were unable to find any viral inclusions or cytopathic changes even in the presence of exudative DAD with hyaline membranes. In such cases, conclusive evidence may be obtained by SARS-CoV-2-specific immunostaining as done by Zhang et al.[44], who were able to demonstrate viral particles in the alveolar epithelium that were almost undetectable on the interstitium and vessel walls.

Almost all studies reported the presence of microthrombi in the small and medium caliber pulmonary vessels, with Grimes et al.[14], Barton et al.[26], Bryce et al [31] and Remmelink et al.[36] being able to find thrombi even in larger pulmonary vessels. Additionally, Tombolini et al.[6], Aguiar et al.[30], Duarte Neto et al.[37] and Dolhnikoff et al.[42] were able to demonstrate naked megakaryocytes in pulmonary and other systemic capillaries, confirming an important pathogenic role of thrombotic microangiopathy in the pathophysiology of COVID 19.

Magro et al.[22] found relevant signs of systemic activation of the complement cascade and detected both SARS-CoV-2 spike glycoproteins and C4d and C5b-9 in the alveolar septa, indicating that activation of the complement cascade might also contribute to the pathogenesis. Varga et al.[43] studied the endothelial damage to various organs and found evidence of lymphocytic endothelitis along with viral inclusions in the endothelial cells of various organs.

Significant cardiac histopathological abnormalities were reported by Elsoukkary S.S. et al.[2], Buja et al.[3], & Bryce et al.[31] and Basso et al.[34]The most consistent finding in most autopsy studies of COVID hearts was a mild lymphocytic myocarditis[2,3,31,34,37,38]; though Eketunde et al.[13] and Bryce et al.[31] also found macrophages in the myocardial interstitium. Bryce et al.[31] also observed evidence of epicarditis along with Schaller et al.[38]; while Buja et al.[3] and Basso et al.[34] documented evidence of lymphocytic pericarditis in their studies. However, contrary to the aforementioned findings, Fox et al.[11] and Tian et al.[35] found little or no evidence of myocarditis in their studies.

While some authors found evidence of individual[11] or multifocal acute myocyte injury[3,13,34], Elsoukkary et.al.[2] found evidence of remote myocardial injury in the form of patchy interstitial fibrosis as well as full blown myocardial infarction. Acute MI in a COVID patient was also reported by Remmelink et al.[36] Bryce et al.[31] & Duarte-Neto et al.[37] reported finding microthrombi in small vessels of the myocardium. Elsoukkary S.S. et al.[2] along with Yan et al.[19] also reported cardiomyocyte hypertrophy. A peculiar finding reported by Menter et al.[24] was the increase in the incidence of senile cardiac amyloidosis in COVID decedents.

Review of available literature on the effect of SARS-COV-2 on other organs revealed discovery of viral particles in various organs including lymph node[31], native[27] as well as transplanted kidneys[43], large intestines[27]and brain[52]. Similar to heart and lung; microthrombi were found in numerous vessels[37] including brain[31], liver (portal venules)[31], kidney (glomeruli)[42] and skin[42]. Some authors also found evidence of deep vein thrombosis[14] with varying grades of pulmonary embolism[29,32].

CONCLUSION:

The study of autopsy histopathology of cardiopulmonary abnormalities in COVID 19 decedents has been a valuable source of information in understanding the pathophysiology as well as modelling the most appropriate therapeutic interventions to combat this new and "novel" disease. The available data point towards ARDS/DAD and thrombotic microangiopathy as the main pulmonary features of COVID 19, with microthrombi also being found in other vital organs like heart, brain, liver and kidney. Unfortunately, in India, not much data is forthcoming on COVID autopsies due to MOF&HW guidelines that prohibit autopsies in COVID positive cases barring a few special circumstances.[7] The need of the hour, therefore, is "defending science in a time of fear and uncertainty"[53] and allowing more autopsy studies to be conducted on COVID 19 patients in the larger interests of the lay public in general and the medical fraternity in particular.

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