Case Report: Hypercoagulopathy as a Severe Long-term Complication of Post SARS-CoV-19 Infection, Autopsy Findings in Three Patients

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Case Report

Keywords: Case report, COVID-19, Autopsy, Hypercoagulopathy, Long-term complication

Posted Date: October 5th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-936635/v1

Abstract

Background: It has been less than two years since the advent of the COVID-19 pandemic, and there are plenty of publications describing the clinical and pathological features of this severe infectious disease, damaging not only lung but also other vital organs. However, the pathologic findings of long-term complications post virus infection have rarely been described.

Case presentation: We are reporting three autopsy cases from patients who had COVID-19 one to six months before death. The patients were all SARS-CoV-2 negative at admission but expired shortly. At autopsy, the first patient showed subacute diffuse myocardial ischemic injury with microthrombi in pericardial small vessels, whereas the second patient showed catastrophic acute and subacute pulmonary infarctions with hemothorax leading to respiratory failure. The third patient showed subacute severe cerebral infarcts in the left middle cerebral artery region.

Conclusions: Our findings suggest the hypercoagulopathy and subsequent vital organ damage may persist beyond the active phase of SARS-CoV-2 infection. It is essential to evaluate and continue monitoring the COVID-19 patients after recovery, so as to identify the ones with vital organ injury in a timely manner and to take the steps to prevent severe consequence of COVID-19 complications.

Introduction

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which started the outbreak in December of 2019 and spread rapidly throughout the world, causing catastrophic situations to human society. On March 11th 2020, COVID-19 was declared a pandemic by the World Health Organization (WHO).[1] One year later, 122 million individuals worldwide have been infected with a death toll reaching to 2.7 million. The majority of infected individuals experience mild common cold-like symptoms and can be managed as outpatients. However, approximately 20% of patients have severe clinical symptoms that require hospitalization and even mechanical ventilation.[2] The risk factors associated with high mortality include hypertension, older age, obesity, as well as male sex with severe cardiovascular comorbidities.[3, 4] The most common presentations include headaches, fever, difficulty breathing, etc., whereas the severe cases show fatal complications of respiratory system (i.e. pneumonia and respiratory failure) and circulatory system (i.e. atrial fibrillation or flutter, hypotension and acute myocardial infarction).[2] Other complications have also been described, including coagulopathy and disseminated intravascular coagulation (DIC), acute liver and renal damage, neuronal injury and encephalopathy, and even rhabdomyolysis.[2, 5]

Despite modern diagnostic technologies, autopsy still has the advantage to examine COVID-19-associated deaths more closely than purely clinical observation, and is essential to understand the biological characteristics and pathogenesis of SARS-CoV-2.[6, 7] The better understanding of COVD-19 pathology may contribute to novel therapeutic strategies and ultimately reduce mortality. Based on autopsy data, the most frequent and direct cause of death in COVID is acute and organizing lung injuries,

with pathologic features of diffuse alveolar damage (DAD), type II pneumocytes hyperplasia, diffuse fibroblasts accumulation along alveolar septa, fibrinous exudate and organizing pneumonia.[8] Thromboembolism is also a significant autopsy finding, presenting as deep venous thrombosis and pulmonary embolism.[6] Cardiovascular injures have also been reported, such as myocarditis, acute myocardial infarction (AMI), and DIC.[9] Nevertheless, our knowledge regarding the pathology in patients recovered from severe COVID-19 patients has been yet insufficient, especially those of long-term complications and disabilities. So far, there is no English literature available on autopsy findings in patients recovered from SARS-CoV-2 infection. Our knowledge under such situation has been mainly obtained from the similar pandemics, such as severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). We are reporting three autopsy cases that were performed on the deceased patients who had been infected with SARS-CoV-2 at least one to six months before death, with a focus on pathological findings of lung, heart and brain, to provide insight of long-term damages on vital organs from COVID-19.

Case Presentation

Patient Information: included below

Clinical Findings: included below

Timeline: Included below
Diagnostic Assessment: Included below

Therapeutic Intervention: Included below

Follow-up and Outcomes: Included below

Case 1

This was a 52-year-old male who was recovered from COVID-19 pneumonia and discharged from the hospital. One month later he came to the emergency department (ED) with 5 days of fever, headache, malaise, general weakness, dizziness, orthopnea, and mild dyspnea on exertion. Virus test was negative for SARS-CoV-2. During his admission, his chest X-ray showed bilateral opacities, and he continued to have spikes of fever. He soon developed multiple cardiac dysrhythmias and shock. The transthoracic echocardiogram showed dilated right ventricle with decreased systolic function. A plan was made for intra-aortic balloon pump placement for afterload reduction and the management of cardiogenic shock. Enroute to the catheterization laboratory, he lost his pulse and went into cardiac arrest. Despite maximal medical efforts, the patient passed away two days after admission.

At autopsy, the most significant macroscopic findings were heavy organs with congestion, including heart (670 g), lungs (right 1360 g and left 1150 g), liver (2370 g), as well as spleen (300 g), suggestive of congestive heart failure. Cross section of the bilateral ventricles showed multiple areas of ill-defined hyperemic changes (Fig. 1A). Microscopically, the bilateral ventricles and septum of heart showed diffuse

interstitial and perivascular inflammatory infiltration, with mainly neutrophils and macrophages, and a minority of lymphocytes. The inflammatory infiltration was most severe in the right ventricular wall, with patchy myocardial hypereosinophilia and necrosis (Fig. 1B and Fig. 1C), and also extended to the endocardium and epicardium. There were microthrombi identified in the small vessels of pericardial adipose tissue (Fig. 1D). These findings were suggestive of a global myocardial ischemic injury. Furthermore, no microorganisms were identified by GMS, PAS, Gram or Warthin-Starry stains. Bilateral lungs showed extensive vascular congestion with intraalveolar edema, hemorrhage and scattered hyaline membrane formation.

Case 2

This was a 35-year-old male with no significant past medical history except alcohol abuse. Per patient his entire family was sick with COVID-19 six months ago. One month later he started to experience intermittent bilateral lower extremity swelling for three to four months. Eventually he presented to ED with worsening dyspnea on exertion over the past few weeks. Upon arrival, he was hypotensive, tachycardic and hypoxic and was started on bilevel positive airway pressure. He was negative for SARS-CoV-2 but anti-viral IgG antibody was positive, and he had first dose of mRNA vaccine 4 days prior to admission. Laboratory studies were significant for lactic acidosis, coagulopathy, abnormal liver enzymes, elevated myoglobin, hyponatremia, and leukocytosis. Chest X ray showed moderate globular enlarged cardiomediastinal silhouette, moderate right pleural effusion, and left retrocardiac opacity. CT angiography of the chest showed multiple occlusive intraluminal filling defects and centrilobular nodular and consolidative opacities. Subsequently the patient developed cardiogenic shock and low-grade fever, and an intra-aortic balloon pump (IABP) was placed. CT brain incidentally showed a small acute infarct of the right cerebellar hemisphere. On the last day of his life the patient suddenly started complaining of sharp left sided chest pain and later was unable to breath. His IABP numbers dropped, and he immediately became unresponsive.

At autopsy, the most significant finding was > 200 ml clotted blood identified in the left lateral thoracic cavity, together with the lateral visceral pleural disruption of the left lower lobe (Fig. 2A). Multifocal hemorrhage was noted on cross sections of the left lower lung, as well as a small area in the right lower lung. Additionally, multiple thrombi in mediate arteries were identified (Fig. 2B). Microscopically, the lower lobe of left lung parenchyma showed alveolar septa infarction with preserved structure and intraalveolar space accumulation of hemorrhage, fibrin deposition, and abundant inflammatory cells (Fig. 2D). There was granulation tissue at the periphery together with reactive pleuritis (Fig. 2E). Large thrombi were confirmed in the arteries of left lower lobe (Fig. 2C). These findings were consistent with histologic changes of subacute pulmonary infarction with rupture. Meanwhile, section from lower lobe of right lung showed alveolar wall necrosis with intraalveolar hemorrhage and fibrin deposition, but no significant neutrophils, macrophages or granulation tissue was noted (Fig. 2F). There was reactive pleuritis noted at the overlying pleura. These findings were consistent with an acute pulmonary infarction with hemorrhage.

Case 3

This was a 48-year-old female who had COVID-19 pneumonia four months ago. Her past medical history was significant for hypertension, heart failure with reduced ejection fraction (15–20%) and obesity. She initially presented to an outside hospital with acute onset of right-sided weakness and dysarthria. CT head was concerning for a left middle cerebral artery (MCA) stroke and CT angiography demonstrated left MCA occlusion, so the patient was transferred to our hospital for escalation of care. SARS-CoV-2 was negative at admission. Mechanical thrombectomy was performed, and her heart failure was treated with diuresis. Patient was discharged for rehabilitation. The next day she developed pulseless electrical activity with intermittent returned of spontaneous circulation. An electrocardiogram showed right bundle branch block. Despite maximum resuscitation efforts, the patient passed away.

At autopsy, gross examination of the brain showed cerebral cortical edema and left cerebral hemisphere bulging, with no uncal or subfalcine herniation present (Fig. 3A). Coronal sections of the cerebral hemispheres showed a blurred grey-white matter junction most prominent in the lateral aspect of the left cerebral hemisphere. There was an ill-defined 4.2 x 4.0 cm swelling lesion with green discoloration located in the lateral aspect of left hemisphere extending from frontal to parietal lobe, involving cortex, subcortical white mater and lateral aspect of basal ganglia (Fig. 3B). There was also another 4.4 x 3.6 cm necrotic and hemorrhagic lesion in the watershed cortical and subcortical region of the left cerebral hemisphere, extending from the parietal to the occipital lobe (Fig. 3C). Microscopically, the two lesional areas showed residual hypereosinophilic neurons admixed with abundant macrophages and granulation tissue (Fig. 3D). These findings were consistent with acute and subacute cerebral infarcts secondary to thrombosis in the left MCA branches. However, no thrombi were identified, likely due to premortem mechanical thrombectomy.

Discussion And Conclusions

We are reporting autopsy findings of three cases with prior history of SARS-CoV-2 infection several months prior to their death. All patients were tested negative for SARS-Cov-2 at the re-admission, but expired shortly. Especially the second patient was a young man with no significant past medical history. Autopsy findings mainly revealed pathological changes in the heart, lungs and brain. One month post SARS-CoV-2 infection, patient of case one showed extensive diffuse acute myocardial ischemic injury with the abundant microthrombi present in the epicardial small vessels, whereas the pulmonary pathologic changes were largely secondary to the heart failure. The cause of death to patient three was mainly due to catastrophic acute and subacute cerebral infarctions. Most interestingly, patient of case two had symptoms one month after the whole family had COVID-19, and he was positive for anti-SARS-Cov-2 IgG antibody five month later at the admission, confirming a past infection. He had pulmonary thrombosis with both acute and subacute hemorrhagic pulmonary infarctions complicated by rupture

with hemothorax leading to respiratory failure and death. The current publications of autopsy findings are mostly from patients died with acute COVID-19. To our knowledge, this is the first autopsy case series describing long-term complications from prior SARS-CoV-2 infection.

COVID-19 primarily affects the lungs, causing interstitial pneumonitis and severe ARDS.[10, 11] The pathologic changes of virus-injured lung can be DAD, diffuse thrombotic alveolar microvascular occlusion, and inflammatory mediator-associated airway inflammation.[12] The patients may have more severely impaired pulmonary diffusion capacities,[13] and the diffuse alveolar injury may cause pleura damage, producing air leakage and interstitial emphysema, even pneumothorax leading to sudden respiratory decompensation.[14] On the other hand, SARS-CoV-2 can induce pulmonary fibrosis by promoting the upregulation of profibrotic signaling molecules, including transforming growth factor-beta (TGF- β).[12] As a consequence, organizing pneumonia and pulmonary fibrosis may happen months after the severe virus infection. We had two additional autopsy cases showing such pathologic changes but are not reporting here. The acute and subacute pulmonary infarction in the patient of case two is a severe long-term complication that has not been reported.

About 20–40% of hospitalized COVID-19 patients showed evidence of myocardial injury, manifested clinically as cardiac chest pain, fulminant heart failure, and cardiac arrhythmias, and is associated with higher morbidity and mortality.[10, 15] The pathology of cardiovascular complications from SARS-CoV-2 infection may include myocarditis, acute myocardial infarction, venous thromboembolisms, acute pericarditis, and cardiac tamponade.[16–18] One cohort study demonstrated that among confirmed COVID-19 hospitalizations 19.7% patients showed cardiac injury, which was an independent risk factor for in-hospital mortality.[19] It is well accepted that the transmembrane protein angiotensin-converting enzyme 2 (ACE2) is the target that S protein of SARS-CoV-2 binds to. It was found that ACE2 is expressed not only on pneumocytes and macrophages in the lung, but also pericytes and cardiomyocytes in the heart.[20] Interestingly, ACE2 is a cardioprotective transmembrane protein whose expression is downregulated by SARS-CoV-2 infection.[15] Direct viral myocardial infection with the virus could be one of the mechanisms of cardiac injury and myocarditis.[15, 21] Surprisingly, the myocardial ischemic injury in our first patient was severe and extensive, and it indicates that the cardiovascular damage and subsequent coagulopathy persist even after SARS-CoV-2 has been cleared and the patient has recovered from COVID-19 pneumonia.

Interestingly, smell and taste disturbances in the absence of nasal obstruction are characteristic of COVID-19.[22] In fact, besides cardiopulmonary damages, up to two-thirds of hospitalized patients show evidence of central nervous system (CNS) damage,[23] with the presentations including anosmia, hypogeusia, stroke, paralysis, cranial nerve deficits, encephalopathy, delirium, meningitis, seizures, and demyelinating disorders such as acute disseminated encephalomyelitis.[24–26] It has been suggested that SARS-CoV-2 virus may enter the CNS via the nasal mucosa and olfactory nerve fibers, or by hematogenous spread, and is capable of infecting endothelial cells, pericytes and probably neurons.[23] Clinical data shows that cerebrovascular stroke has been the most common neurological abnormality

seen among COVID-19 patients.[26, 27] The blood clots in COVID-19 patients can not only lead to myocardial infarctions, pulmonary embolism and renal failure, but also can be present in both cerebral arteries and cerebral veins. The precise mechanism for cerebrovascular complications in such patients is not known, but there are some suggested mechanisms, such as exaggerated cytokine response triggered by the virus, and / or the resulting hypercoagulopathy and formation of blood clots in blood vessels throughout the body and the brain.[25, 28] However, brain autopsy studies of such cases mainly show mild and non-specific picture, such as acute hypoxic injury, hemorrhage, and mild to moderate non-specific inflammation, with no evidence for CNS damage directly caused by SARS-CoV-2, such as neurotropism or meningitis/encephalitis.[29, 30] Detecting of SARS-CoV-2 in human brain tissue by immunohistochemistry or PCR has been inconsistent.[22, 31] In our reported patient three, the catastrophic brain pathology was acute and subacute infarcts, with no significant evidence for meningitis or encephalitis identified.

Contrary to the common long-term pulmonary complications, the patient one showed diffuse myocardial ischemic injury with microthrombi present in the epicardial microvasculature. This was unusual because the patient had COVID-19 one month earlier and the microthrombi were only present in epicardial vasculature, whilst absent in lung and kidney vasculatures, making the status of DIC unlikely. The patient was negative for SARS-CoV-2 at the second admission. It is unclear the cause of microthrombi, but likely due to endothelial lesion and microvascular damage post SARS-CoV-2 infection. The patient two was also unusual for catastrophic lung hemorrhagic infarction complicated by rupture and hemathorax, in the setting of thrombi identified in the pulmonary arteries. Additional cerebellar infarct was also identified in this patient, indicating high risk of coagulopathy. This young man did not have comorbidities but did have COVID-19 vaccination four days before admission. However, his symptoms were present long before the vaccination, making the vaccine as a cause of thrombosis less likely. The last case showed catastrophic acute and subacute brain infarctions.

Microthrombosis and/or microvascular coronary dysfunction has been posited to be one of the mechanisms of acute organ damages during COVID-19.[15] The excessive inflammation, hypoxia, and DIC could cause both venous and arterial thromboembolism.[32] On the other hand, SARS-CoV-2 may cause vascular thrombosis directly through aggravating the vessels and indirectly by causing cytokine cascade leading to hypercoagulable state, which has been manifested as pulmonary embolisms, deep vein thrombosis, arterial thrombosis of the abdominal small vessels, as well as ischemic and hemorrhagic strokes.[33] In fact, it has been postulated that the continuous and uncontrolled activation of the immune system caused by the viral infection, with subsequent excessive cytokine release or “cytokine storm” could play a pivotal role in brain stroke and damage.[27] However, it is unexpected and remains unclear that the hypercoagulable state and risk for infarction may persist much longer than previous expected period after patients recovered from COVID-19.

The pandemic of COVID-19 has been only less than two years, and it remains largely unclear the long-term health consequences post SARS-CoV-2 infection. It has been reported that 3 to 6 months after acute infection, 87.4% COVID-19 survivors commonly show clinical sequalae, such as general symptoms (i.e.

fatigue or muscle weakness, sleep difficulties, and anxiety or depression), respiratory symptoms (i.e. dyspnea, chest pain, cough, excessive sputum and throat pain), and cardiovascular-related symptoms (i.e. tachycardia, palpitation, and hypertension).[13, 21, 34, 35] Based on the data from previous coronavirus outbreaks such as SARS and MERS, it can be speculated that some patients may experience long-term respiratory complications of the infection, including chronic cough, fibrotic lung disease, bronchiectasis, and pulmonary vascular disease.[11, 36, 37] With millions of COVID-19 confirmed cases world wide, there is growing concerns regarding long-term infection related chronic respiratory symptoms or fibrotic diseases among recovered individuals, as well as calling for formulation of relevant prevention and intervention strategies.[12, 37] Our autopsy findings indicate the necessity of early evaluation and continued monitoring of respiratory and cardiac damages, as well as coagulative status after hospitalization, so as to identify patients with vital organ injury in a timely fashion and take the steps to prevent severe COVID-19 complications.[10]

In conclusion, the vital organs may be damaged directly from SARS-CoV-2 infection and also from the massive immune storm that the host exerts to fight against the virus. Furthermore, in some patients the damage and subsequent repairing may persist beyond the clearing of the virus, which may cause long-term complications and functional impairment of vital organs, such and lung, heart and brain. Our autopsy findings have shown that some patients may experience severe post infection complications leading to death. It is important to follow these patients regularly, screen for signs of potential complications, and initiate prophylactic therapeutic strategies to prevent severe long-term complications from happening.

Abbreviations

ACE2
Angiotensin-converting enzyme 2
CNS
Central nervous system
DAD
Diffuse alveolar damage
DIC
Disseminated intravascular coagulation
COVID-19
Coronavirus disease 2019
ED
Emergency department
IABP
Intra-aortic balloon pump
MCA
Middle cerebral artery

MERS
Middle East respiratory syndrome
SARS
Severe acute respiratory syndrome
SARS-CoV-2
Severe acute respiratory syndrome coronavirus 2
WHO
World Health Organization

Declarations

Patient Perspective

Not applicable

Ethics declarations:

Ethics approval and consent to participate

Not applicable: autopsy case report

Consent for publication

Not applicable: autopsy case report with no identifiable personal information

Competing interests

The authors declare that they have no competing interests.

Funding

None

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Figures

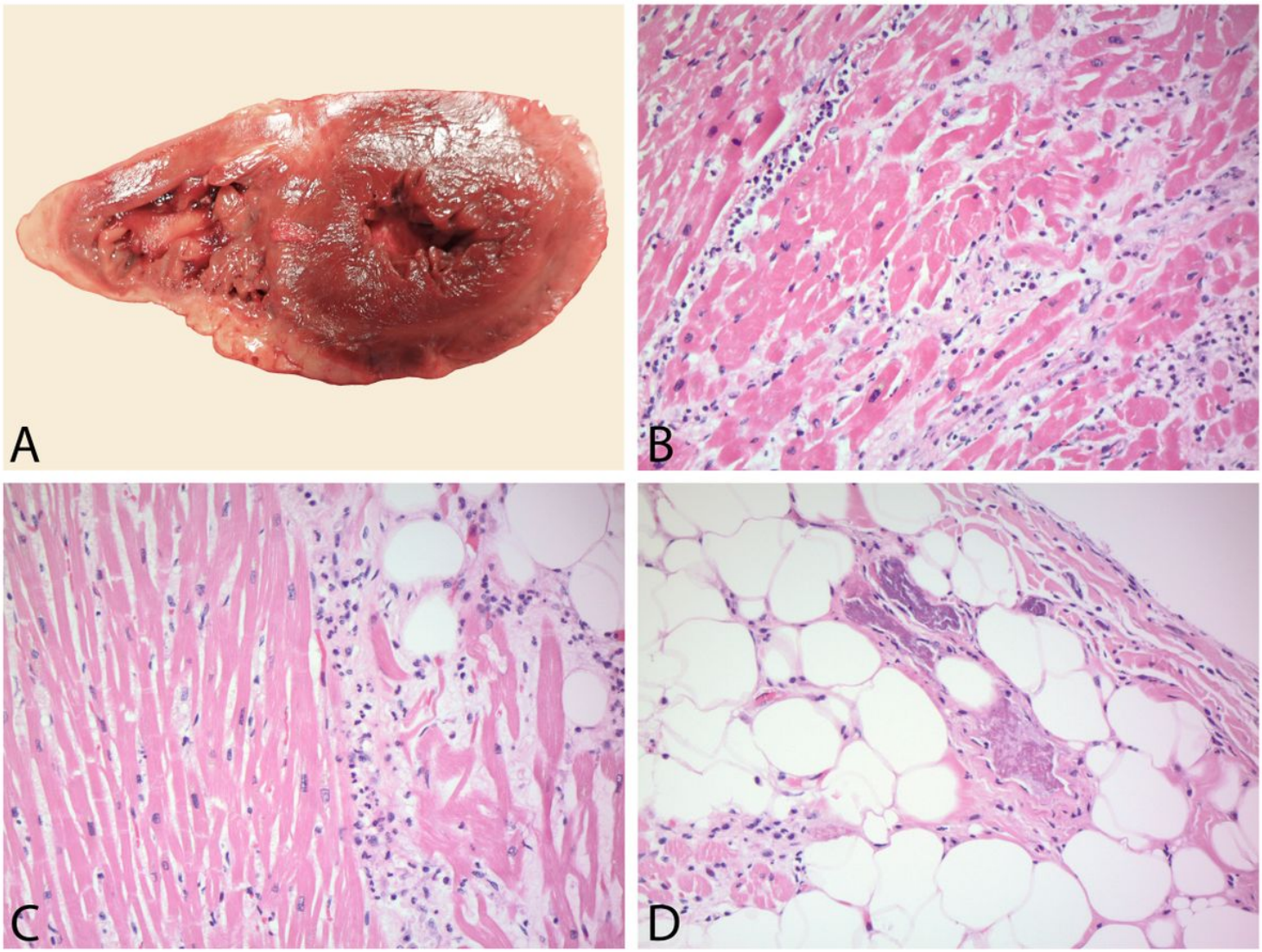

Figure 1

Heart of patient of case one shows (A) Cross section of bilateral ventricles with multifocal ill-defined areas of eosinophilic changes; (B) Section from left ventricular wall with interstitial inflammatory infiltration, mainly neutrophils and macrophages, with cardial myofibers showing hypereosinophilia and

focal necrosis; (C) Section from right left ventricular wall with interstitial and subepicardial inflammatory infiltration, mainly neutrophils and macrophages, with cardial myofibers showing hypereosinophilia and focal necrosis; (D) Section from epicardium with thrombi present in the small vessels.

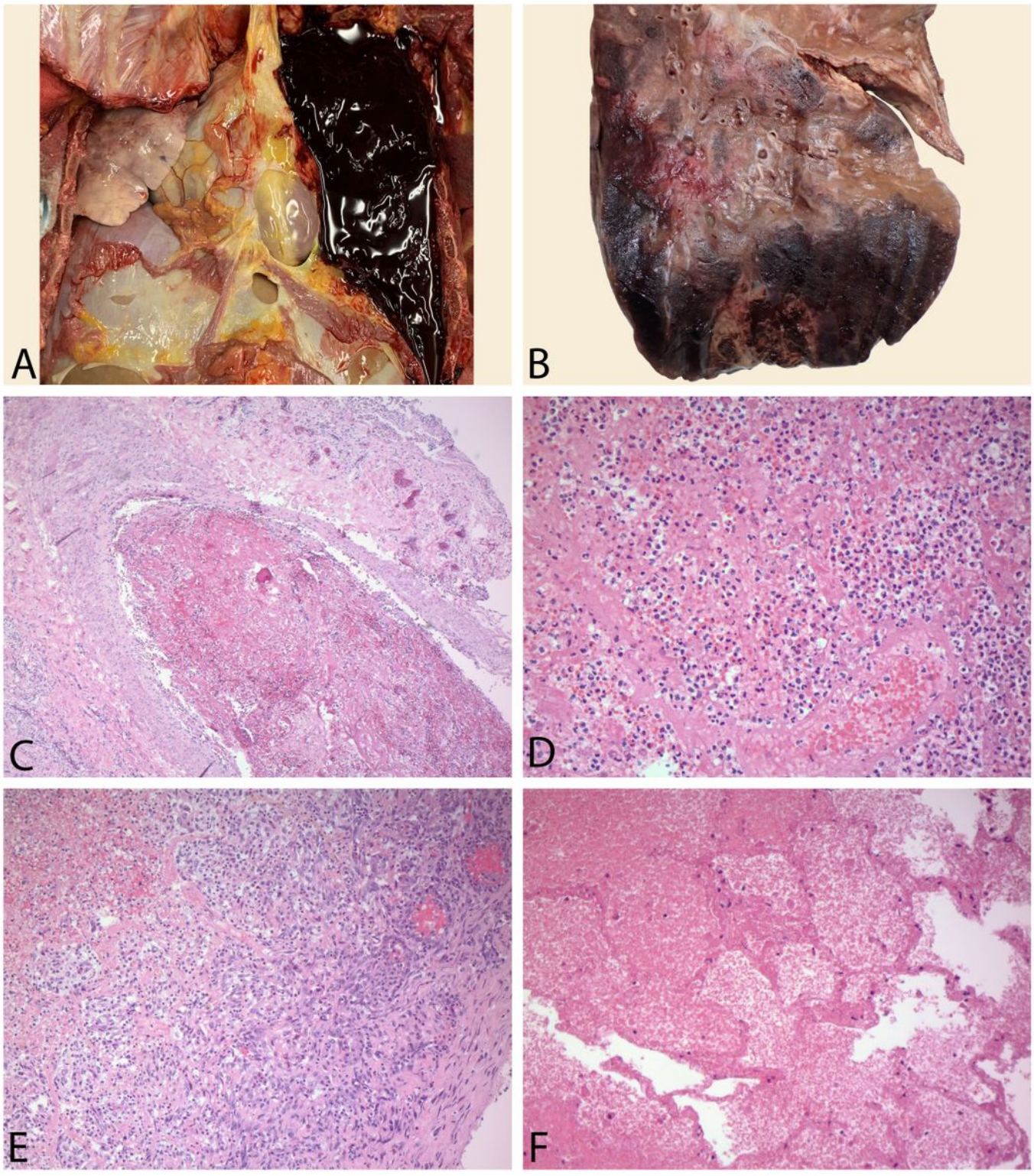

Figure 2

Lungs of patient of case two show (A) Catastrophic hemothorax in the left lateral thoracic cavity; (B) Cross section of left lung with multifocal areas of hemorrhage in the lower lobe, mostly at the periphery,

with parenchymal rupture at the inferior aspect, as well as multiple thrombi present in the pulmonary mediate sized vessels; (C) One large thrombi present in an artery of left lobe; (D) Section from left lower lobe with massive parenchymal infarct and intraalveolar inflammatory cell accumulation; (E) Section from the periphery of hemorrhagic region showing granulation tissue formation with reactive pleuritis; (F) Section from hemorrhagic region of right lower lobe with massive parenchymal infarct and intraalveolar hemorrhage, with no significant inflammatory accumulation.

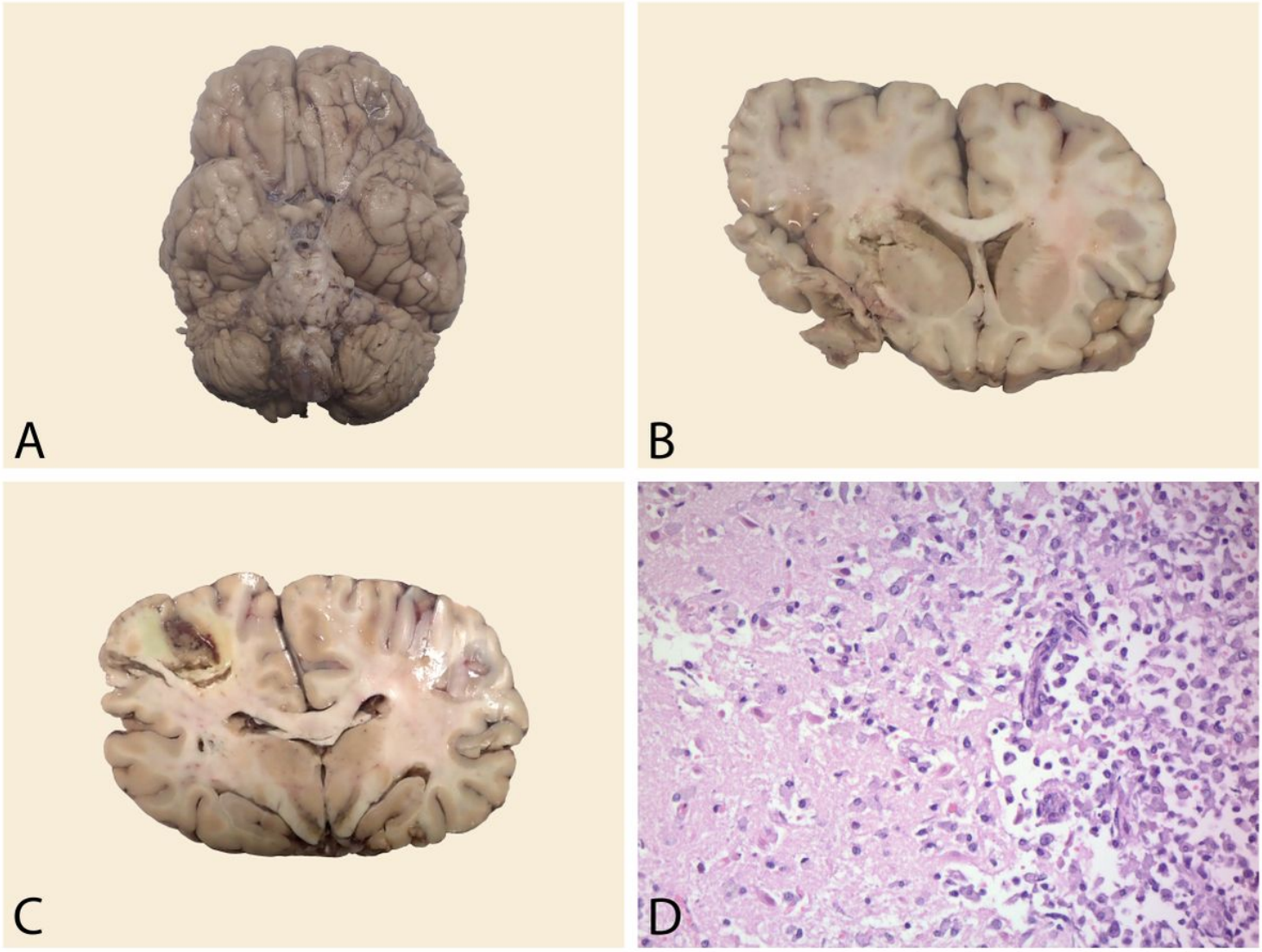

Figure 3

Brain of patient of case three shows (A) Swelling of the lateral aspect of left cerebral hemisphere, with no evidence for uncal or tonsillar herniation identified; (B) Coronal section with blurred gray-white matter junction and an ill-defined swelling lesion in the lateral aspect of left cerebral hemisphere, involving gray-white matter and lateral aspect of left basal ganglia; (C) Coronal section with blurred gray-white matter junction and a necrotic hemorrhagic lesion in the watershed area of left cerebral hemisphere; (D) Section of both lesions with residual hypereosinophilic neurons admixed with abundant macrophages and granulation tissue.