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Human Pathology Reports 27 (2022) 300595

Contents lists available at ScienceDirect

Human Pathology Reports

journal homepage: www.journals.elsevier.com/human-pathology-reports

Case Report

Hypercoagulopathy as a severe Long-term complication of post SARS-CoV-19 infection

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ARTICLE INFO

Keywords:
COVID-19
Autopsy
Hypercoagulopathy
Long-term complication

ABSTRACT

Two years since the advent of the COVID-19 pandemic, it is time to discuss the long-term complications post virus infection. We are reporting three autopsy cases from patients who had COVID-19 one to six months before death. All three patients were 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. 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 continue monitoring the COVID-19 patients after recovery, so as to identify those with vital organ injury in a timely manner and to take necessary steps to prevent severe consequences of COVID-19 complications.

1. Introduction

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak of which started in December of 2019 and spread rapidly throughout the world. On March 11th 2020, it was declared a pandemic by WHO [1]. By the end of 2021, 288 million individuals worldwide have been infected, with a death toll reaching 5.44 million. The majority of infected individuals experience mild common cold-like symptoms. However, approximately 20% of patients have severe clinical symptoms that require hospitalization and even mechanical ventilation [2]. Based on autopsy data, the most frequent causes of death in COVID are acute and organizing lung injuries [3], as well as thromboembolism, cardiovascular injures and DIC [4]. Nevertheless, our knowledge regarding the pathology in patients recovered from severe COVID-19 has been yet insufficient, especially in those of long-term complications and disabilities. Herein we are reporting three autopsy cases performed on deceased patients who had been infected with SARS-CoV-2 one to six months before death, with a focus on pathological findings of the lungs, heart and brain, to provide insight of long-term damages on vital organs from COVID-19.

2. Case presentation

Case 1. *This was a 52-year-old male who was hospitalized and recovered from COVID-19 pneumonia. One month later he came to the emergency department (ED) with fever, headache, general weakness, orthopnea, and mild dyspnea on exertion. PCR SARS-CoV-2 was negative and chest X-ray showed bilateral opacities. He soon developed multiple cardiac dysrhythmias and shock. The transthoracic echocardiogram showed dilated right ventricle with decreased systolic function. He passed away two days after admission.*

At autopsy, the heavy organs (Table 1) with congestion suggested congestive heart failure. Sections of the bilateral ventricles showed multiple areas of ill-defined hyperemic changes (Fig. 1A). Microscopically, the bilateral ventricles and septum showed diffuse interstitial and perivascular inflammatory infiltration, mainly neutrophils and macrophages, most severe in the right ventricular wall, with patchy myocardial hypereosinophilia and necrosis (Fig. 1B and Fig. 1C). Microthrombi were identified in the small vessels of pericardial adipose tissue (Fig. 1D). These findings were suggestive of a global myocardial ischemic injury. No microorganisms were identified by special stains. Lungs showed extensive vascular congestion with intraalveolar edema,

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https://doi.org/10.1016/j.hpr.2022.300595
Received 10 January 2022; Received in revised form 27 January 2022; Accepted 28 January 2022
Available online 3 February 2022

Table 1
Additional information of the three cases.

	Past Medical history	Pre-mortem History	Additional Autopsy Findings
Case 1	1. 52-year-old male 2. No significant past medical history except obstructive sleep apnea and colonic polyps. 3. COVID-19 pneumonia diagnosed one month prior to the presentation, fully resolved without residual symptoms.	1. Presented to ED with 5 days of fevers, headache, malaise, general weakness, dizziness, orthopnea, and mild dyspnea on exertion. 2. COVID-19 test: negative for SARS-CoV-2 RNA by PCR. 3. Chest X-ray: bilateral opacity. 4. Transthoracic echocardiogram: dilated right ventricle with decreased systolic function. 5. Lab tests at the admission: increased D-Dimer (4.32 mg/L FEU), normal PT-patient (12.3 secs), normal PT-INR (1.13); normal Troponin I (0.02 ng/mL); decreased platelet (109 K/uL) 6. Lab tests before death: Mildly increased PT-patient (13.4 secs); mildly increased PT-INR (1.24); severely increased Troponin I (0.58 ng/mL); decreased platelet (129 K/uL) 7. Passed away two days after admission.	1. Heavy organs with congestion: • Heart 670 g • Right lung 1360 g • Left lung 1150 g • Liver 2370 g • Spleen 300 g 2. Lungs: • Diffuse alveolar damage • Early chronic bronchitis • No pulmonary embolism or capillary microthrombosis identified
Case 2	1. 35-year-old male. 2. No significant past medical history except alcohol use. 3. He started to experience intermittent bilateral lower extremity swelling one month after his entire family was sick with COVID-19, and his symptom persisted for four to five months before he presented to ED.	1. Presented to ED with worsening dyspnea on exertion over the past few weeks. 2. COVID-19 test was negative for virus RNA, but positive for anti-viral IgG antibody. 3. Lab test at the admission: increased D-Dimer (17.76 mg/L FEU); increased PT-patient (17.7 secs) and PT-INR (1.72); normal aPTT (27.5 secs); normal Troponin I (0.02 ng/mL); normal platelet (203 K/uL) 4. Lab tests before death: increased PT-patient (22.9 secs) and PT-INR (2.26); increased aPTT (60.6 secs); normal Troponin I (0.01 ng/mL); normal platelet (233 K/uL) 5. CT brain: a small acute infarct of the right cerebellar hemisphere. 6. Passed away 11 days after admission.	1. Hepatosplenomegaly: • Liver 2400 g • Spleen 230 g • Liver with centrilobular necrosis 2. Heart • Normal weight 295 g • Diffuse endocardial ischemic injury 3. Kidneys: • Normal weight, combined 370 g • No microthrombi or tubular necrosis identified.
Case 3	1. 48-year- old female. 2. Past medical history also included hypertension, heart failure with reduced ejection fraction (15–20%) and obesity. 3. COVID-19 pneumonia four months prior to the admission.	1. Presented to ED with acute onset of right-sided weakness and dysarthria. 2. An electrocardiogram showed right bundle branch block (RBBB). 3. COVID-19 test: Negative for SARS-CoV-2 RNA by PCR 4. Lab tests at the admission: normal fibrinogen (274 mg/dL); normal PT-patient (11.8 secs) and PT-INR (1.12); normal aPTT (26.6 secs); normal Troponin I (0.01 ng/mL); normal platelet (245 K/uL) 5. Lab tests before death: not performed except normal platelet (303 K/uL) 6. Passed away 10 days after admission.	1. Heart: • Cardiomegaly 500 g • Acute myocardial ischemic injury, diffuse, bilateral ventricular walls and interventricular septum • Mild atherosclerosis without calcification, left anterior descending coronary artery 2. Lungs: • Right 640 g; Left 600 g • Extensive congestion with intraalveolar edema of bilateral lungs • No embolus/tumor identified 3. Liver: • Weight 1530 g • Moderate macrovesicular steatosis and mild portal inflammation • Cholelithiasis

Reference Ranges:
- PT-patient 9.5–13.2 secs; PT-INR 0.89–1.26
- aPTT 23.0–33.0 secs
- Platelet count 150–399 K/uL
- Troponin I 0.00–0.09 ng/mL
- Fibrinogen 190–395 mg/dL; D-Dimer 0.00–0.60 mg/L FEU
- Heart weight 270–360 g (male); 200–280 g (female)
- Lung weight right 360–570 g, left 325–480 g
- Liver 1500–1800 g
- Spleen weight 100–155 g
- Kidney combined weight 230–440 (male); 240–350 g (female).

hemorrhage, and scattered hyaline membrane formation.

Case 2. *A 35-year-old male with no significant past medical history contracted COVID-19 six months ago, started to experience intermittent bilateral lower extremity swelling, and eventually presented to ED with worsening dyspnea on exertion, hypotension, tachycardia and hypoxia. He tested negative for SARS-CoV-2 but positive for anti-viral IgG antibody. Chest X-ray showed moderate globular enlarged cardiomediastinal silhouette, right pleural effusion, and left retrocardiac opacity. Chest CT angiography showed multiple occlusive intraluminal filling defects. Subsequently the patient developed cardiogenic shock. On the last day of his life the patient suddenly started complaining of sharp left sided chest pain and was unable to breathe, and soon became unresponsive.*

At autopsy, there was 200 ml clotted blood in the left lateral thoracic cavity, with the visceral pleural disruption of the left lower lobe (Fig. 2A). Multifocal hemorrhage was noted in the left lower lung and a small area in the right lower lobe. Additionally, multiple intravascular thrombi were identified (Fig. 2B). Microscopically, the left lower lobe

showed alveolar septal necrosis with intraalveolar accumulation of blood, fibrin and inflammatory cells (Fig. 2D). There was granulation tissue at the periphery with reactive pleuritis (Fig. 2E). Large thrombi were confirmed in the arteries of left lower lobe (Fig. 2C). These findings were consistent with subacute pulmonary infarction with rupture. Meanwhile, the right lower lobe showed alveolar wall necrosis with intraalveolar hemorrhage and fibrin deposition, but no inflammation or granulation tissue (Fig. 2F), consistent with an acute pulmonary infarction.

Case 3. *This was a 48-year-old female who had COVID-19 pneumonia four months prior to presentation. She presented with acute onset of right-sided weakness and dysarthria. CT angiography demonstrated left middle cerebral artery occlusion. PCR SARS-CoV-2 was negative at admission. Mechanical thrombectomy was performed and her heart failure was being treated with diuresis. The next day she developed pulseless electrical activity. An electrocardiogram showed right bundle branch block, and shortly she passed away.*

At autopsy, the brain showed cerebral cortical edema and left cerebral hemisphere bulging, without uncal or subfalcine herniation (Fig. 3A). Coronal sections showed a blurred grey-white matter junction with an ill-defined 4.2 × 4.0 cm swelling lesion with green discoloration in the lateral aspect of the left frontoparietal lobe, involving cortex, subcortical white matter and lateral aspect of the basal ganglia (Fig. 3B). There was another 4.4 × 3.6 cm necrotic lesion in the watershed cortical and subcortical region of the left parietooccipital lobe (Fig. 3C). Microscopically, the two lesions showed residual hypereosinophilic neurons admixed with abundant macrophages and granulation tissue (Fig. 3D), consistent with acute and subacute cerebral infarcts.

3. Discussion

Acute COVID-19 primarily affects the lungs, causing interstitial pneumonitis and severe acute respiratory distress syndrome [5]. About 20–40% of hospitalized COVID-19 patients also show evidence of myocardial injury, with the pathologic features of myocarditis, acute myocardial infarction, and acute pericarditis [6,7]. Additionally, up to two-thirds of hospitalized patients show evidence of CNS damage [8]. However, brain autopsy studies mainly show mild and non-specific pictures, such as acute hypoxic injury, hemorrhage, and mild to moderate non-specific inflammation [9,10].

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 re-admission, but expired shortly. Autopsy findings mainly revealed pathological changes in the heart, lungs and brain. Patient 1 showed extensive diffuse acute myocardial ischemic injury with microthrombi present in the epicardial small vessels. 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 cause of the microthrombi was unclear, but may be related to microvascular damage post SARS-CoV-2 infection. Patient 2 was also unusual for catastrophic lung hemorrhagic infarction complicated by rupture and hemothorax, with thrombi identified in the pulmonary arteries, and was noteworthy for being a young man with no significant past medical history. Patient 3 showed catastrophic acute and subacute brain infarcts. Furthermore, all three patients had prothrombin time (PT) and partial thromboplastin time (PTT) within normal range or mildly increased at admission (Table 1). Unfortunately, no family history or genetic data related to hypercoagulopathy was addressed from the patients' charts. The current publications of autopsy

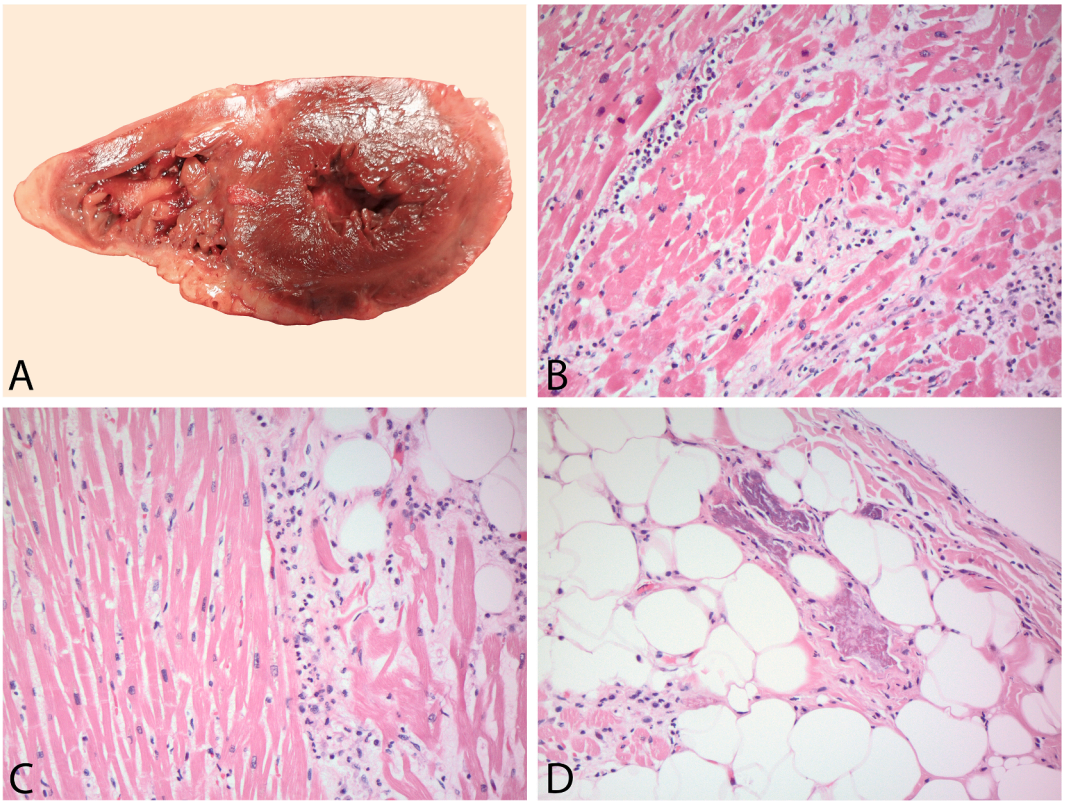

Fig. 1. Heart of Patient 1 shows (A) Cross section of bilateral ventricles with multifocal ill-defined areas of eosinophilic changes; (B) Section from left ventricular wall with interstitial inflammatory infiltration, mainly neutrophils and macrophages, with cardial myofibers showing hypereosinophilia 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.

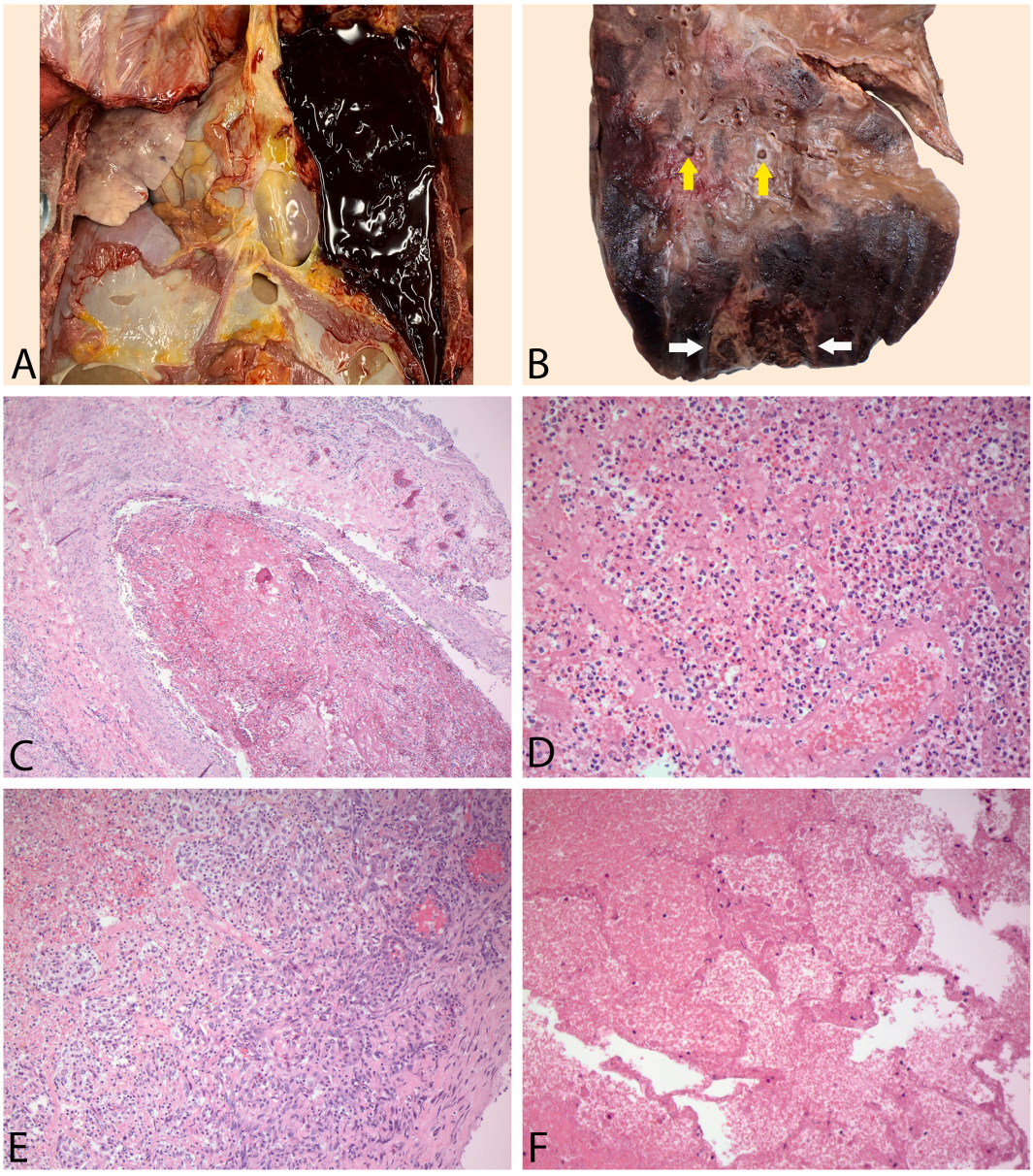

Fig. 2. Lungs of Patient 2 show (A) Catastrophic hemothorax in the left lateral thoracic cavity; (B) Cross section of left lung with multifocal areas of hemorrhage in the lower lobe, mostly at the lower periphery, with parenchymal rupture at the inferior aspect (white arrows), as well as multiple thrombi present in the pulmonary medium sized vessels (yellow arrows); (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 infiltrate; (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 infiltrate. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

findings are mostly from patients who 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.

Microthrombosis and/or microvascular coronary dysfunction has been posited to be one of the mechanisms of acute organ damage during COVID-19 [11]. The excessive inflammation, hypoxia, and DIC could cause both venous and arterial thromboembolism [12]. 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 [13]. 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 [14]. However, it is unexpected and remains unclear if the hypercoagulable state and risk for infarction persists longer than the previous expected period after patients recovered from COVID-19.

After two years of prevalence, the long-term health consequences post SARS-CoV-2 infection have started to appear. It has been reported that months after acute infection, 87.4% of COVID-19 survivors commonly show clinical sequelae, such as general symptoms (i.e. fatigue, anxiety and depression), as well as respiratory and cardiovascular-related symptoms [15–18]. With millions of COVID-19 confirmed cases worldwide, there are growing concerns regarding infection related chronic disabilities and the calling for formulation of prevention and intervention strategies [19,20]. Our autopsy findings indicate the necessity of early evaluation and continued monitoring 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.

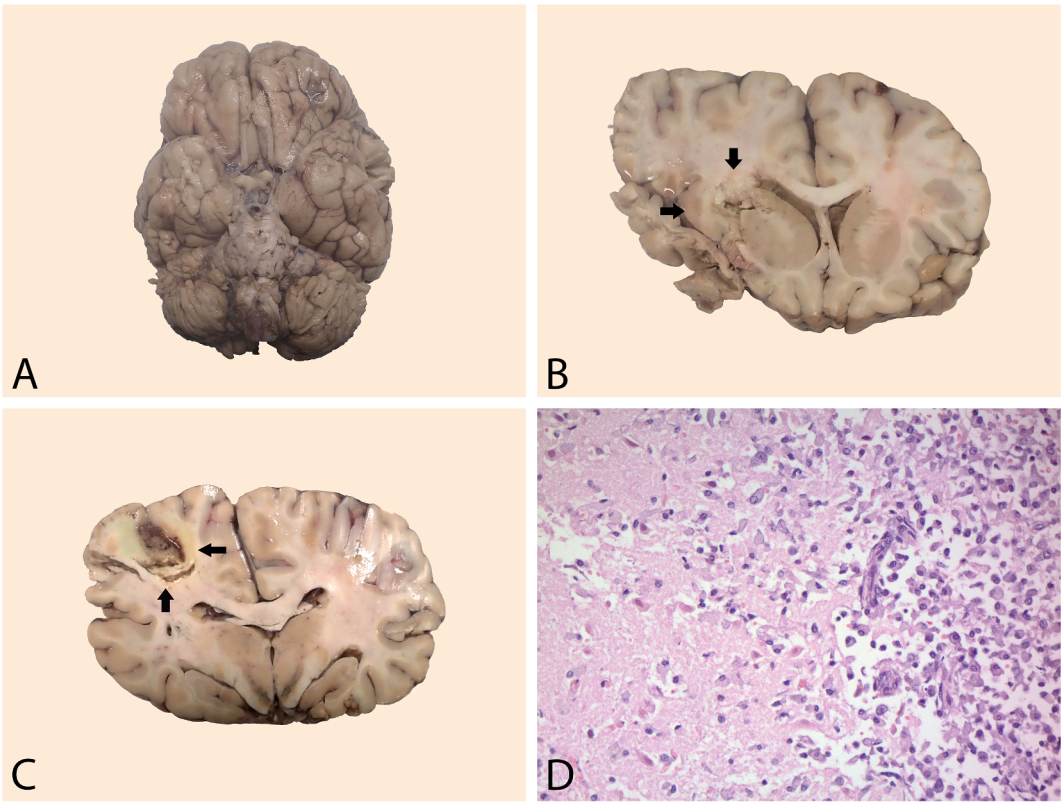

Fig. 3. Brain of Patient 3 shows (A) Swelling of the lateral aspect of left cerebral hemisphere, with no evidence for uncal or tonsillar herniation identified; (B) Coronal section with blurred gray-white matter junction and an ill-defined swelling lesion in the lateral aspect of left cerebral hemisphere, involving gray-white matter and lateral aspect of left basal ganglia (black arrows); (C) Coronal section with blurred gray-white matter junction and a necrotic hemorrhagic lesion in the watershed area of left cerebral hemisphere (black arrows); (D) Section of both lesions with residual hypereosinophilic neurons admixed with abundant macrophages and granulation tissue, suggestive of subacute infarct.

Ethics statement

This is an autopsy report of deidentified data with no harm or prejudice to the patients or patients' families.

Patient consent statement

This is a report of three autopsy cases with de-identified data. Based on the policy of Human Pathology Case Reports, no consent is needed.

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