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Large Cerebellar Stroke in a Young COVID-19–Positive Patient: Case Report

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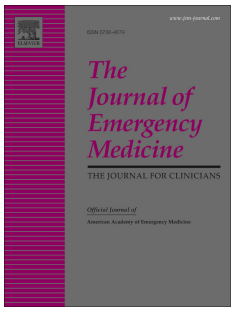

Large cerebellar stroke in a young COVID-19 positive patient

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Cover Sheet

Article Title: **Large cerebellar stroke in a young COVID-19 positive patient**

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Large cerebellar stroke in a young COVID-19 positive patient

Case Report

ABSTRACT

Background: Coronavirus Disease 2019 (COVID-19), caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), most frequently presents with respiratory symptoms such as fever, dyspnea, shortness of breath, cough, or myalgias. There is now a growing body of evidence that demonstrates that severe SARS-CoV-2 infections can develop clinically significant coagulopathy, inflammation, and cardiomyopathy, which have been implicated in COVID-19 associated cerebrovascular accidents (CVAs).

Case Report: We report an uncommon presentation of a 32-year-old man who sustained a large vessel cerebellar stroke associated with a severe COVID-19 infection. He presented with a headache, worse than his usual migraine, dizziness, rotary nystagmus, and dysmetria on exam but had no respiratory symptoms initially. He was not a candidate for thrombolytic therapy or endovascular therapy and was managed with clopidogrel, aspirin, and atorvastatin. During hospital admission he developed COVID-19 related hypoxia and pneumonia, but ultimately he was discharged to home rehabilitation.

Why Should an Emergency Physician Be Aware of This? We present this case to increase awareness among emergency physicians of the growing number of reports of neurological and vascular complications such as ischemic CVAs in otherwise healthy individuals who are diagnosed with SARS-CoV-2 infection. A brief review of the current literature will help elucidate possible mechanisms, risk factors, and current treatments for CVA associated with SARS-CoV-2.

INTRODUCTION

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the primary cause of the ongoing Coronavirus Disease 2019 (COVID-19) pandemic. COVID-19 most frequently presents with respiratory symptoms such as fever, dyspnea, cough, or myalgias.[1] There is now mounting evidence that demonstrates that SARS-CoV-2 infections can give rise to a wide range of neurological symptoms. These include headache, seizures, dizziness, ataxia, encephalitis, ageusia, anosmia, neuralgia, Guillain-Barre syndrome, Acute disseminated encephalomyelitis, and cerebrovascular accidents (CVAs).[2-5]

Strokes in young, healthy adults are less commonly observed and comprise approximately 10-15% of the overall number of strokes in the United States.[6] However, strokes have also been observed in patients diagnosed with COVID-19.[2-5,7] Observational research has demonstrated that SARS-CoV-2 infection has been associated with a coagulopathic state and a variety of prothrombotic sequelae.[8-14] We report an unusual case of a large cerebellar CVA in a young man who presented to a community emergency department (ED) with a headache and dizziness and without initial respiratory symptoms that are typical of COVID-19 infections.

CASE REPORT

A 32-year-old man with a history of tension type migraine headache presented to a community ED with headache, generalized weakness, dizziness, nausea, and vomiting which started at 0800 the previous day. The patient described a severe, sudden onset headache located over the left temple and sudden acute vertigo. His headache was constant, and more severe than

his normal migraine headaches. The patient denied fever, changes in vision, rash, or neck stiffness. He had no chest pain, palpitations, shortness of breath, dyspnea upon exertion, or cough. He had not tried any medication and reported no palliative or provoking symptoms. He denied any tobacco use, illicit drug or prescription drug use. He was living with his parents who both had reportedly tested positive for COVID-19.

Upon arrival to the ED, his initial vital signs were blood pressure 130/89 mmHg, heart rate 77, respiratory rate 26 breaths per minute, oxygen saturation 100% on room air, and body mass index (BMI) of 28.7 (overweight). Overall, the patient was well-appearing and in mild distress. He was alert and oriented to person, place, year, and situation. His rapid alternating movements and gait were normal. His neurological examination was notable for mild decrease sensation over the left temple, left upper extremity ataxia and dysmetria, and rotary nystagmus. The patient's vertigo and nystagmus worsened with the Dix-Hallpike maneuver when his head was turned to the left. He reported mild relief of symptoms with the Epley maneuver.

His initial complete blood count had white count of 6.85 x 10^3/µL(4.80-10.7 x 10^3/µL), hemoglobin 15.7 g/L (14.1-16.6 g/L), hematocrit 48.7% (41.0-48.0%), platelet count 366 x10^3/µL (130-400 x10^3/µL), and lymphocytes 9.7% (18.0-45%). The differential had an elevation of atypical lymphocytes 8.0% (0.0-2.0%). The comprehensive metabolic panel was unremarkable except for glucose 121 mg/dL (70-110 mg/dl) and a slight elevation in the alanine aminotransferase (AST) at 88 U/L (0-55U/L). The SARS-CoV-2 nasopharyngeal PCR test Abbott ID NOW COVID-19 assay (Abbott Diagnostics Scarborough, Inc, Scarborough, ME) was positive. Additionally, his D-dimer was elevated to 2443 ng/mL (0-230 ng/mL), c-reactive protein (CRP) was elevated to 1.7 mg/dL (0.0-0.9mg/dL), and lactic dehydrogenase (LDH) was elevated to 860 U/L (313-618U/L). His alcohol level was <10mg/dL (0-10mg/dL) and the urine

drug screen was negative for opiates and illicit drugs. A computerized tomography scan of the head (CT head) without contrast was performed.

Prior to the final read of the CT head without contrast, the tele-neurology service was also consulted due to the patient's vertigo, ataxia, and rotary nystagmus. The patient was treated for a possible complicated migraine headache, or benign positional peripheral vertigo with ketorolac 30 mg IV, metoclopramide 10 mg IV, and dexamethasone 6 mg IV in the ED. Despite treatment, the patient's vertigo, ataxia, and rotary nystagmus was persistent and severe. The results of the CT head without contrast (Figure 1) then showed a large left cerebellar non-hemorrhagic infarction. The radiologist also noted an 8 mm hyperattenuated lesion within the left anterolateral aspect of the foramen magnum, which was concerning for a thrombosed aneurysm within the region of the left posterior inferior cerebellar artery, with an associated high-density focus in the distal left vertebral artery. The basilar artery was unremarkable. Geographic hypoattenuation throughout the left inferior cerebellar hemisphere was also noted, concerning for ischemic change (See Figure 1). A Magnetic Resonance Imaging (MRI) Brain with and without contrast was performed shortly thereafter confirming the same cerebellar infarct (See Figures 2 and 3).

Hospital Course

The tele-neurology service was consulted again due to the findings of both the CT head and the MRI head without contrast (Figure 1 and Figure 2), which were concerning for left sided cerebellar infarct. Because his stroke symptoms started more than 48 hours prior to arrival, thrombolytics and endovascular interventions were not recommended. The National Institute of Health Stroke Scale was not recorded during his ED stay or his discharge. He was admitted and

started on clopidogrel 600mg, aspirin 324 mg, and 80 mg of atorvastatin. An initial screening chest x-ray showed no evidence of pneumonia, consolidation, or any pulmonary edema (Figure 4). However, on day five of admission, he developed symptoms consistent with hypoxia secondary to COVID-19 pneumonia and was given supplemental oxygen, but did he did not require invasive ventilation. The patient did receive a course of remdesivir when he developed COVID-19 pneumonia. The basic metabolic panel and the CBC were performed throughout his admission within the first two weeks. However, the CBC differential was only performed sporadically. No other laboratory abnormalities were noted except for the consistently elevated D-dimer (Figure 5), elevated WBC and lymphopenia on day 5 when the patient was found to have COVID-19 pneumonia. Figure 6 shows the a sharp increase of his WBC to 15.6 x 10^3/µL(4.80-10.7 x 10^3/µL) with 79.8% (44-72%) neutrophils and 8.6% (18.0-45%) lymphocytes on day 5 which normalized by day 10 to WBC of 7.86 x 10^3/µL (4.80-10.7 x 10^3/µL).

Additional laboratory screening for was positive only for phosphatidyl serine immunoglobulin M antibodies (IgM), but all other antiphospholipid syndrome (APS) antibodies were negative. All other coagulopathic laboratory tests such as protein C and protein S, antithrombin, factor V, von Willebrand Factor, and factor VIII were normal. Additionally, the Lipoprotein (a) cholesterol was < 10mmol/L (normal < 75 mmol/L). The echocardiogram and bubble study was unremarkable. His symptoms of nystagmus and vertigo continued to improve and he was discharged on clopidogrel 75 mg daily and atorvastatin 80 mg daily. He was also ambulatory with a walker on day 13 awaiting transfer to a rehabilitation facility.

Routine laboratory values were not reported daily after day 17 of admission. Only SARS-CoV-2 and D-dimer were monitored every other day until one week prior to discharge. Nearby

rehabilitation facilities required two serial negative SARS-CoV-2 tests for acceptance. However, the patient continued to have positive tests for SARS-CoV-2 while continuing his rehabilitation at the hospital. He was discharged on day 26 with his symptoms markedly improved while awaiting home rehabilitation. There were no additional records from outpatient follow up to indicate that he had any additional laboratory tests to further investigate coagulopathies or vasculitis.

DISCUSSION

Ischemic stroke is one of the more serious neurologic complications seen in patients with COVID-19 infection and has been observed more commonly in patients older than 55 years who have significant comorbidities.[2-5,9-17] Retrospective studies in Wuhan, China have found to have an incidence of 2% to 5% CVA in COVID-19 patients.[2,15] Ischemic strokes were more commonly observed in COVID-19 patients than hemorrhagic strokes.[3,7,15] In a case series of six COVID-19 patients by Morassi and colleagues there were four (67%) ischemic strokes and two (33%) hemorrhagic strokes.[3] Li and colleagues have found that of their 219 patients with confirmed SARS-CoV-2, 11 (5.0%) had developed new onset of CVA following COVID-19 infection. Of these patients, 10 (90.9%) were diagnosed with ischemic stroke and 1 (9.1%) had intracerebral hemorrhage.[15]Ashrafi and colleagues found six COVID-19 patients under the age of 55 who were diagnosed with ischemic CVA.[7] These patients presented with either altered mental status, hemiplegia, hemiparesis, or dysarthria. Excluded from the study were patients with any patients who had abnormal echocardiograms. Five (83.3%) of the six patients had strokes involving the middle cerebral artery and one patient with a basilar artery stroke. One of the patients died from the stroke.[7]

A growing amount of evidence shows that patients with COVID-19 develop clinically significant coagulopathy, inflammation, and cardiomyopathy which have been implicated in associated CVAs.[15-18]

Pathophysiology and mechanisms of COVID-19 stroke

Patients with ischemic strokes and severe SARS-CoV-2 infection are observed to have clinically significant prothrombotic states.[7-17] Recently, abnormal D-dimer, prothrombin time (PT), activated partial thromboplastin time (aPTT), platelets, fibrinogen, antithrombin activity, factor V, von Willebrand Factor, and factor VIII in findings have been found in patients with severe COVID-19.[18,19] A retrospective study by Helms and colleagues compared the number of significant thrombotic complications such as arterial thrombosis, pulmonary embolisms, and CVAs in COVID-19 patients with acute respiratory distress syndrome (ARDS) versus those with non-COVID-19 ARDS. They observed that significant thrombotic complications were more likely to be diagnosed in 27 (18%) of 150 of the patients with COVID-19 ARDS versus the 14 patients (6%) of the 233 non-COVID-19 ARDS patients with an OR 3.4 [1.7–7.3], $p < 0.001$.[19]

The exact pathogenesis of this hypercoagulopathy has yet to be fully elucidated, but it is postulated that it is a multifactorial process that also includes the complement pathway.[20-22] In prior studies relating to SARS-CoV (SARS), it was observed that elevated complement (C3) activation exacerbates ARDS. Prior studies of SARS suggest that C3 inhibition may decrease the risk of inflammatory lung complications of SARS-CoV-2.[20-21] Elevated levels of complement have been observed in patients with severe SARS-CoV-2 infection. There is some histopathological evidence to suggest that complement-driven endothelial damage on various organs due to SARS-CoV-2 infection.[20-23] Vascular endothelium that is damaged by SARS-CoV-

2 can activate the complement system and cause an over-activation of the systemic pro-inflammatory response. This is hypothesized to be part of a catastrophic positive feedback loop with the coagulation system which in turn leads to an over-activation of the complement system.[16,20-23] The positive feedback of the pro-inflammatory response has been observed in severe COVID-19 cases.[20-23]Additionally, known risk factors such as diabetes, hypertension, coronary artery disease, and obesity that have been associated with pre-existing vascular endothelial damage could also make patients with these comorbidities especially vulnerable to severe COVID-19 and associated vascular complications.[22]

The most common laboratory evidence of coagulopathy in severe COVID-19 is found with elevated D-dimer.[8,14,17-19,22-24] Guan and colleagues found 1,099 COVID-19 patients with a D-dimer of 0.5 mg/L or higher were more frequently observed in patients with severe disease than in those without (60% vs. 43%, p=0.002).[24] In a retrospective analysis of 138 hospitalized patients, Wang and colleagues observed that there was a 2.5-fold increase in D-dimer level in ICU patients (n=36) compared to non-ICU (n=102) patients ($p < 0.001$).[8] Wang and colleagues also observed that those with severe COVID-19 who died, had D-dimers greater that 1000mg/L compared to non-survivors who had D-dimer levels less than 500mg/L ($p<0.05$).[8] In the retrospective cohort analysis in New York, 32 (0.9%) of the 3556 COVID-19 positive patients with strokes had higher peak D-dimer versus stroke patients without COVID-19. Reportedly, 65% of these strokes were cryptogenic.[25]

Severe SARS-CoV-2 infection is also associated with increased systemic inflammation from infection mediated endothelial injury through interleukin (IL-6) and tumor necrosis factor alpha (TNF-α), which triggers excessive thrombin production leading to microthrombi and microvascular dysfunction.[10,26-28] Additionally, angiotensin converting enzyme type 2 (ACE2)

receptors found on endothelial cells of the blood-brain-barrier can allow for viral entry into the nervous system and attack the vasculature of the nervous system causing endothelitis.[12,21,26-28] SARS-CoV-2 infection stimulates ACE2, thus increasing ATII, which causes microcirculatory vasoconstriction and endothelial dysfunction with consequent ischemia and apoptosis.[12,20-21,26-28]

Patients with infections due to viral illnesses have had antiphospholipid antibodies which may have contributed to major coagulopathic complications.[29-31] Standard antiphospholipid syndrome (APS) classification includes thrombosis or pregnancy morbidity and the presence of one laboratory criterion lupus anticoagulant (LAC), anticardiolipin antibodies (aCL) or beta2-glycoprotein I antibodies (aβ2GPI). Then, the presence of these antibodies are measured again 12 weeks after the initial testing.[32] Recently, there have been reports that have found temporary increase of antiphospholipid antibodies in critically ill COVID-19.[9-11,13,30,31] Zhang and colleagues reported confirmed severe COVID-19 cases were found to have aCL and aβ2GPI immunoglobulin A and immunoglobulin G.[11] In critically ill COVID-19 patients with thrombotic events, the prevalence of antiphospholipid antibodies is estimated to be between 45% to 91%.[9,11-13] The presence of these various antiphospholipid antibodies have also been observed in reported cases of COVID-19 patients with large vessel cerebral infarcts in multiple vascular territories.[9-11,13]

Although not part of the formal APS criteria, a review of literature has demonstrated that even anti-phosphatidylserine (aPS) immunoglobulin M (IgM) antibodies have been associated with significant thrombotic events.[33,34] Our patient in the case had an elevation of aPS IgM in his serum. These aPS IgM have been observed as transient, but have been implicated in patients with severe COVID-19 patients with major thromboembolic complications.[31,33] In a recent review of 172 hospitalized COVID-19 patients, Zuo and colleagues measured levels of aCL, aβ2GPI, and

aPS/PT. They found that 50% of the hospitalized patients had become transiently aPL positive. Of the 172 hospitalized patients, 18% were positive for aPS/PT IgM.[31] In their systematic review, Sciascia and colleagues found that in 7000 patients from 48 studies, anti-phosphatidylserine IgM had increased the risk of thrombotic events with an odds ratio [OR] 2.3; 95% confidence interval [CI] 1.72-3.5).[33] In comparing anti-prothrombin antibodies versus aPS antibodies, Sciascia and colleagues observed aPS antibodies appeared to have stronger risk factor for thrombosis both arterial and/or venous than aPT (OR 5.11; 95%CI 4.2-6.3 and OR 1.82; 95%CI 1.44-2.75, respectively).[33]

Additionally, there are several proposed mechanisms in SARS-CoV-2 infection that could contribute to cardiomyopathy and thus ischemic stroke. In their research, Wang and colleagues observed that acute cardiac injury can come from direct invasion of SARS-CoV-2. Direct invasion causes inflammation and myocarditis.[14] Similarly, inflammation produced from SARS-CoV-2 could be implicated in pericarditis. Myocarditis, myopericarditis, and pericarditis due to COVID-19 can predispose one to cardiac arrhythmias which contribute to strokes.[14,35,36] In addition, stress and cytokine storm can also cause dysrhythmias which predispose patients to embolic strokes.[14,35,36]

Epidemiology and profile of those with COVID-19 strokes

Several retrospective cohort studies have estimated the incidence of COVID-19 associated strokes to be 2.5% to 6% of the total number of COVID-19 patients.[13,36-,39] According to several retrospective cohort studies, COVID-19 associated CVAs were more frequently observed in patients older than 55 years and with stroke risk factors due to the increased risk of

having diabetes, hypertension, hypercholesterolemia, peripheral vascular disease, prior strokes, obesity, and cardiac disease. [3,7,13,15,22,28-36-38]

Cohort studies of CVAs associated with COVID-19 infection found that they often occurred in a much younger population. Ashrafi and colleagues reported that their patients had a mean age of 43.5 years ± 7.42 (range 33–53 years). In this cohort, half were male who presented with respiratory symptoms and hypoxic with O2 saturation below 92% on room air and half of the patients had comorbidities such as hypertension and or diabetes.[7] Oxley and colleagues reported five patients under the age of 50 with no prior medical history presenting with large vessel strokes where four of the five patients had an elevated D-dimer.[40]

Potential treatment and therapy of COVID-19 stroke

Because of the mechanism of increased coagulation, it is hypothesized that anticoagulants such as enoxaparin should help decrease coagulopathic complications in COVID patients. There are interim guidelines that support the routine use of low molecular weight heparin in patients with coagulopathy.[14,25] Yaghi and colleagues reported that a randomized trial of therapeutic anticoagulation versus prophylactic anticoagulation is underway to test for safety and efficacy of enoxaparin in patients with severe COVID-19 infection associated coagulopathy.[24] In the case of ischemic stroke, if patients are within the given three hour time frame of stroke onset, thrombolytic therapy or thrombectomy should be considered.[14,41]

Limitations

We cannot establish strong causal effect of a coagulopathic state with the outcome of ischemic stroke in our patient. Migraine, in itself, increases the risk of stroke, but this is more

likely in women.[42] Furthermore, we do not know if our patient truly had an underlying primary coagulopathy. Although, he did not report having a concomitant connective tissue disease or a coagulopathy to suggest that could have contributed to his hypercoagulopathic state and stroke.

Our patient had an elevation of anti-phosphatidyl serine antibodies which does not meet the diagnosis of antiphospholipid syndrome. However, there are no records to re-evaluate for the presence of antiphospholipid syndrome and the anti-phosphatidyl serine antibodies in a 12-week span. However, recent research does seem to observe a transient elevation of anti-phosphatidyl serine antibodies in COVID-19 patients and that these patients do have a higher risk for coagulopathic complications including strokes.[30,31,36] Additionally, the elevation in D-dimer and the presence of anti-phosphatidyl serine antibodies could be an indicator for a hypercoagulopathic state in COVID-19 patients that may have led to the patient's stroke like in other cases.[9-12,36]. Regardless, we postulate that the SARS-CoV-2 infection may have been an important precipitating factor for thrombosis which resulted in our patient's cerebellar CVA.

Why Should an Emergency Physician Known About This?

We report an unusual case of a large ischemic cerebellar stroke in a young man with no other prior medical history than migraine headaches who did not present with primary respiratory symptoms of COVID 19 at the onset of his course. Although rare, this case should raise awareness among emergency physicians of SARS-CoV-2 in otherwise low risk patients who present with a high clinical suspicion of CVA given the coagulopathic risk.

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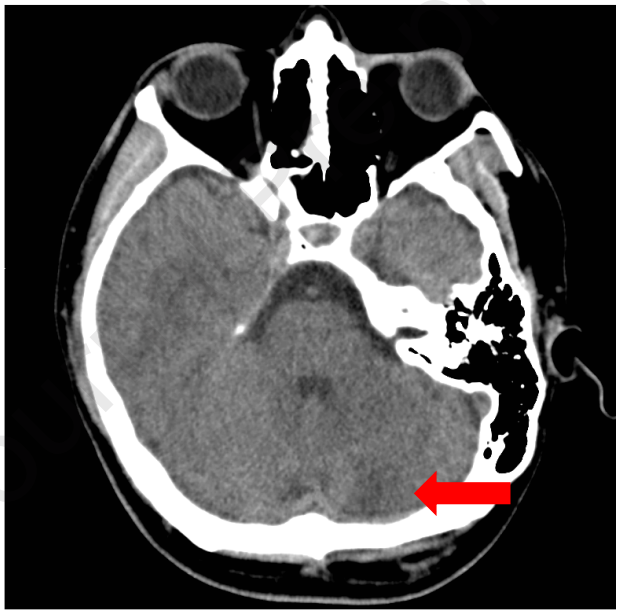
386 **Figures**

387

388 **Figure 1. CT head without contrast.** There is a moderately large patchy area of low attenuation
389 involving the inferior two thirds of the left cerebellum (arrow) suggesting an acute non
390 hemorrhagic infarction of the left posterior cerebral artery territory. There appears to be a
391 thrombus within the left vertebral artery. There is no acute intracranial hemorrhage, no white
392 matter ischemic changes, or demyelination identified.

393



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396 Figure 2. MRI Brain without contrast shows the acute non-hemorrhagic infarction of the inferior
397 two thirds of the left cerebellum. There is a moderately large acute non-hemorrhagic infarction
398 of the inferior two thirds of the left cerebellum (arrow) corresponding to the left posterior
399 inferior cerebellar artery (PICA) territory. There is no acute intracranial hemorrhage.

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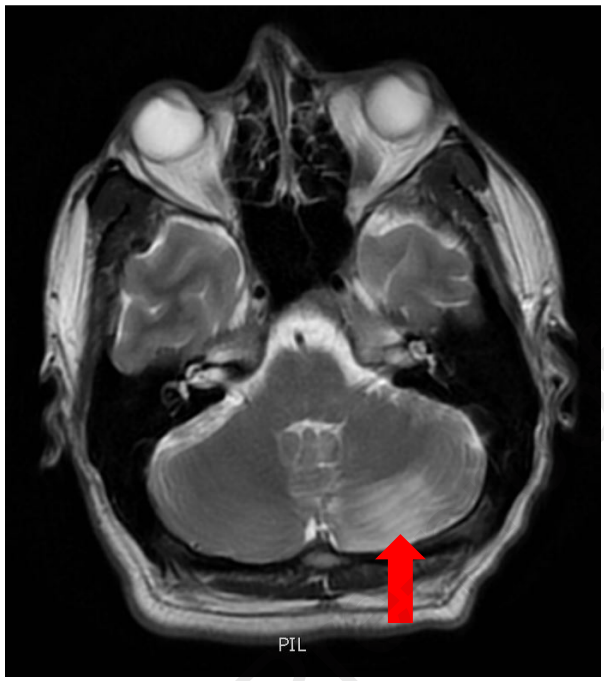

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404 Figure 3. MRI head without contrast, Diffusion Weight Imaging (DWI) demonstrates a
405 moderately large area of true diffusion restriction involving the lower two-thirds of the left
406 cerebellum (circled) consistent with acute non-hemorrhagic cerebellar infarction. No acute
407 intracranial hemorrhage. There is no hemosiderin deposition evident within the brain
408 parenchyma.

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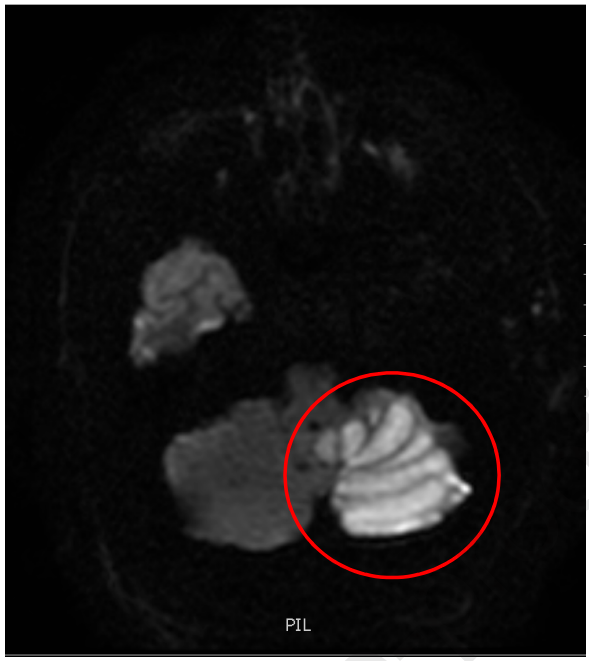

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413 Figure 4. Anterior Posterior view chest x-ray is negative for COVID pneumonia on admission.

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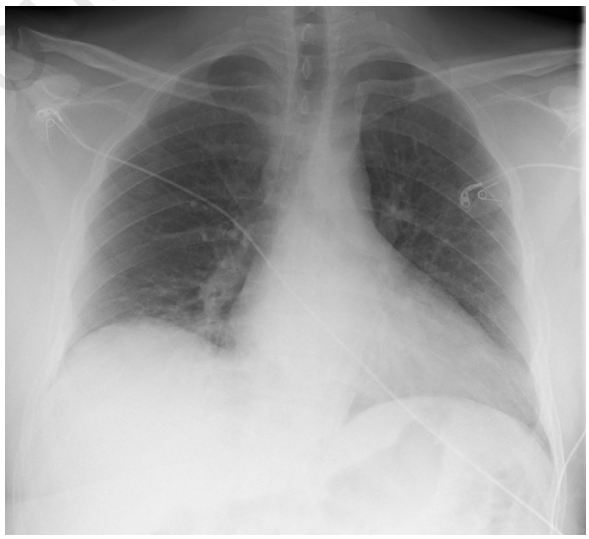

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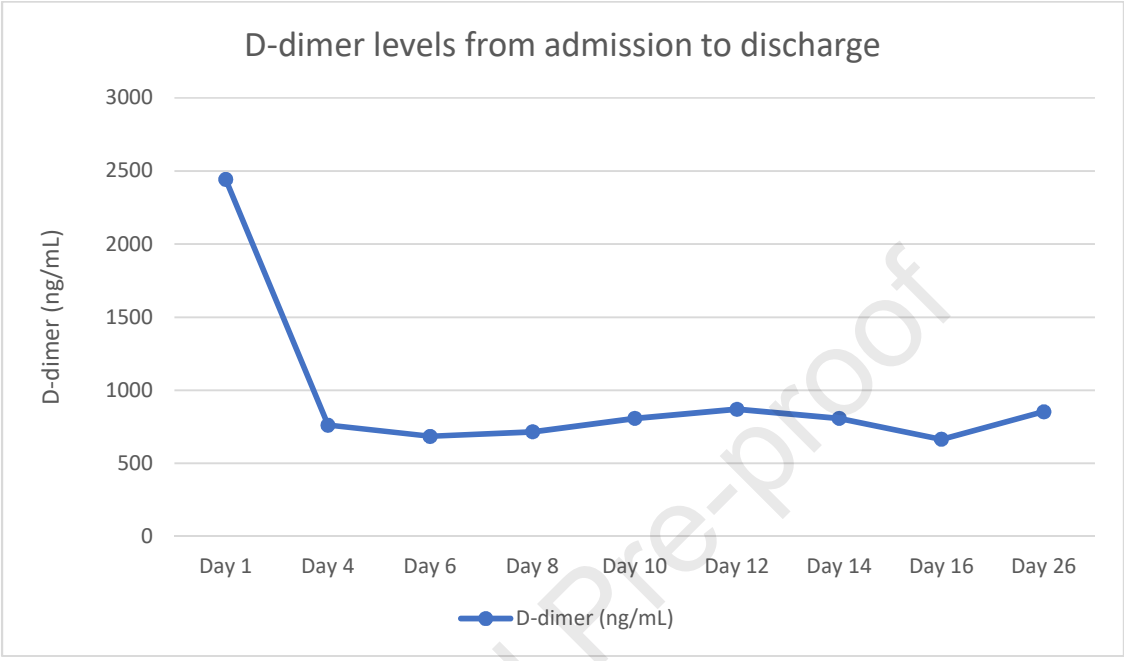
418 Figure 5. D-dimer from admission to discharge.



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421

422 Figure 6. White blood cell count (WBC) from admission day 1 to day 17. The increase of WBC
423 correlates with the patient's diagnosis of hypoxia secondary to Coronavirus Disease of 2019
424 (COVID-19) pneumonia on day 5.

425

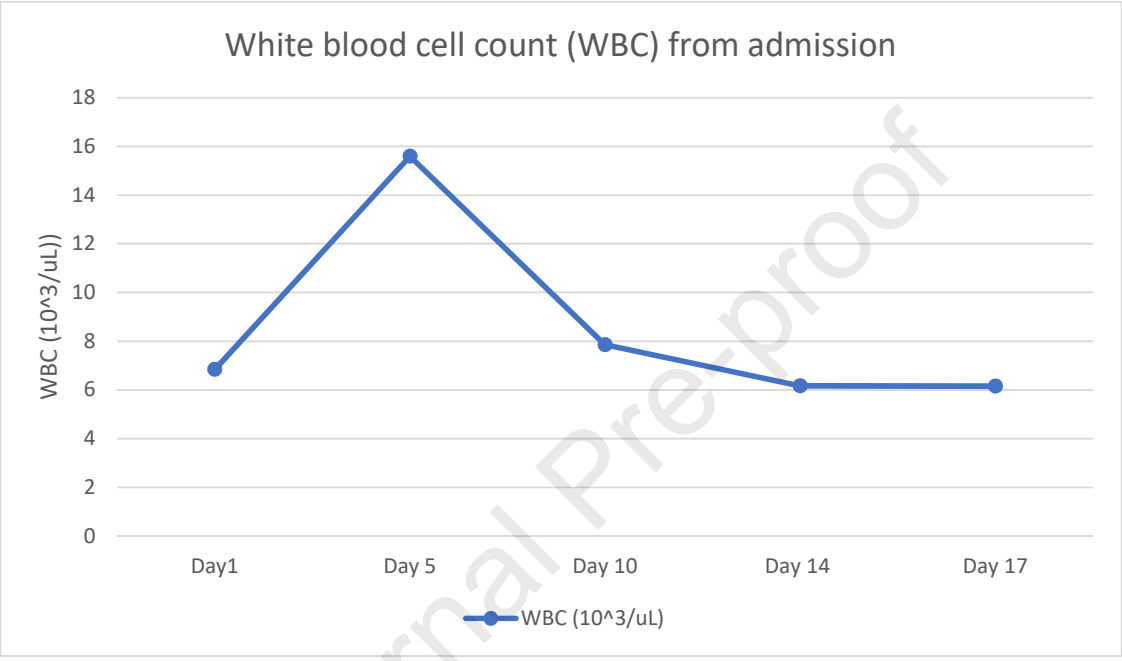

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Figure 5. D-dimer from admission to discharge.

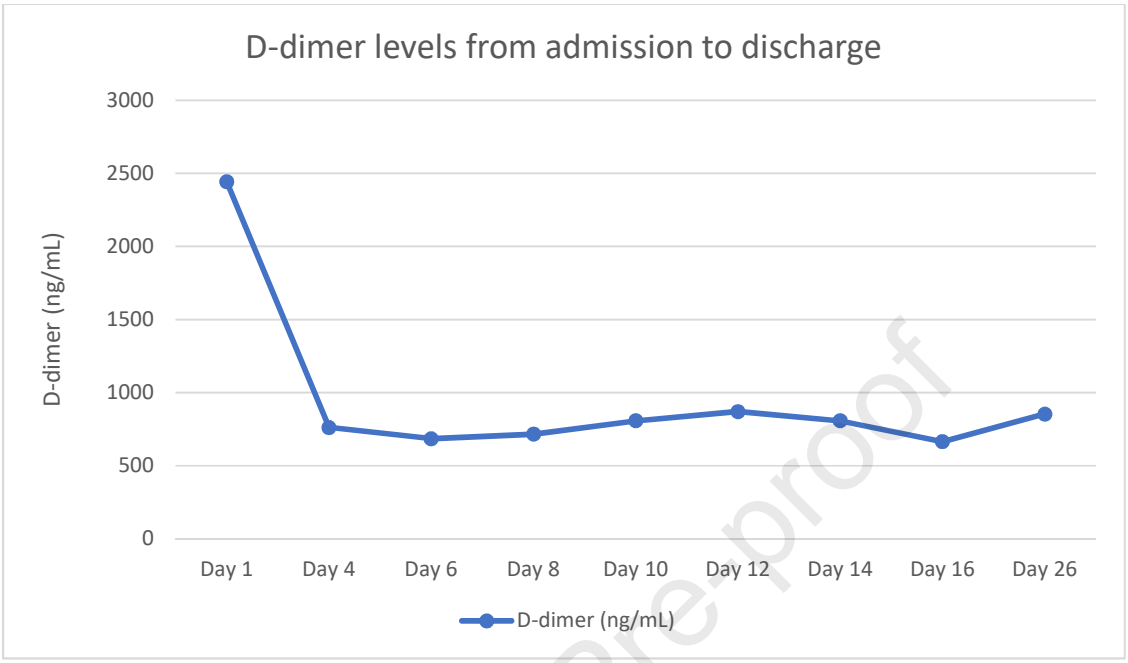

Figure 6. White blood cell count (WBC) from admission day 1 to day 17. The increase of WBC correlates with the patient's diagnosis of hypoxia secondary to Coronavirus Disease of 2019 (COVID-19) pneumonia on day 5.