

Case Reports of Cerebral Sinus Venous Thrombosis in COVID-19 Patients

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Case Report

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Abstract

Background: The outbreak of Coronavirus disease 2019 (COVID-19) has started in China since December 2019 and expanding worldwide rapidly with cases of respiratory tract infection and multiple system involvement. Neurological manifestations are not exempted following the reports from various sources about Ischemic and haemorrhagic stroke related to COVID-19, but the reports about cerebral sinus venous thrombosis (CSVT) are still rare.

Case presentation: We would like to report two cases of cerebral sinus venous thrombosis in COVID-19 patients following the respiratory manifestations with profound haematological and coagulation disarrangement triggered by COVID-19 and these are assumed as underlying mechanism. These two cases also have different course of disease and outcome which are interesting.

Conclusions: CSVT is one of neurological complication and COVID -19 manifestation that can have grave prognosis, if this involves the brainstem venous drainage. Thrombogenesis and coagulation cascades are prolonged despite successful alteration to negative result of severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) reverse transcription polymerase chain reaction (rt-PCR) test. Therefore, monitoring neutrophil to lymphocyte ration (NLR), D-dimer level, fibrinogen and C-reactive protein (CRP) is paramount as well as indicators of poor prognosis.

Background

In December 2019, the cases of SARS-CoV-2 infection has been reported to cause severe pneumonia in several patients in Hubei Province, China (1). Most of people has fever, fatigue, and dry cough as first symptoms of Coronavirus Disease 2019 (COVID-19) (2–4), but now the symptoms are growing to neurologic manifestation (5). Patients with severe infection of Severe Acute Respiratory - Coronavirus 2 (SARS-COV2) commonly has neurologic manifestation that directly proportional to older age patients with comorbid such as hypertension, diabetes, or cardiac disease (5). The cerebrovascular disease (CVD) related to COVID-19's incidence is related with cerebral ischemic or hemorrhagic manifestation (6). Several reports show the cerebral venous thrombosis related to COVID-19 with variant presentation (7–9).

We report two cases of cerebral sinus venous thrombosis (CSVT) associated with COVID-19. The patients composing our initial experience developed profound neurologic injury secondary to cerebral sinus venous thrombosis (CSVT) with SARS-CoV-2 infection confirmed by real time reverse transcriptase polymerase chain reaction (rt-PCR) assay. The COVID-19 caused by the SARS-COV2 virus activates the inflammatory cascade and thrombotic pathways by binding the angiotensin-converting enzyme 2 (ACE2) receptors of endothelial cells (10), that leads to a hypercoagulable state proved by the increase of D-dimer (3,11). High level of D-dimer indicates high thrombus formation (12). Two cases of CSVT below were having neurological manifestation of COVID-19.

Case Presentation

First case, 58-years old female admitted to our Hospital in Bali, Indonesia on 5th of August 2020 due to altered of consciousness, seizures and left sided limbs weakness with fever, malaise, and dry cough 3 days before admission. The patient had a history of hypertension since the last 1 year. Upon examination T 36⁰C; HR 109 beats/min; RR 22 breaths/min; BP 170/ 110mmHg; O2 saturation, 99% on simple mask; lethargic; GCS E4V4M6; the equal size of bilateral pupils with reactive to light; left central facial paresis, hemiplegia left extremities.

The result of laboratory tests was: blood glucose, 254 mg/ dL; HbA1C 6.5%, white blood cells (WBC) 14/L, Neutrophil-Lymphocyte Ratio (NLR) 33; erythrocyte sedimentation rate (ESR) 93mm/h, D-dimer 21,176 ng/mL and fibrinogen 446 mg/dL. Liver function, electrocardiograms were normal. Reverse transcription polymerase chain reaction (RT-PCR) from nasal swab was positive for SARS-COV2. The laboratory results are listed in the table 1

Head Contrast Computed Tomography showed cerebral edema at right parietal lobe (Figure 1B). There were hyperdense veins and sinuses at right parietal lobe area, superior sagittal sinus (SSS), and bilateral transverse sinuses (TS) suggesting a cerebral sinus venous thrombosis (CSVT) (Figure 1B, C, D) with sign of venous hypertension. CT venography (CTV) confirmed CSVT at SSS, TS bilateral, sigmoid sinus bilateral (Figure 1E, F). Thorax CT scan revealed ground glass opacity subpleural bilateral with fibrotic appearance in left lung (Figure 1A).

She was treated previously as a status of convulsion and regain her consciousness soon after the seizure ceased. During her treatment of COVID 19, Enoxaparin 60mg subcutaneous twice a day was administered for 5 days. At day-5 of treatment D-dimer was decreased to 2,092 ng/mL and the grade form hemiparesis improved to grade 2. Enoxaparin was decided to be continued until we reach the normal D-dimer or the patient negative for the COVID-19.

Second case, 72-years old male was referred to our department due to sudden decrease of consciousness. He was being treated as Covid-19 with ARDS for 10 days with history of fever, dry cough, and shortness of breath 7 days before admission. The patient had no previous history of hypertension or diabetes. During previous treatment, heparin was administered for 10 days and then was halted due to good recovery based on clinical and laboratory findings, until He got deteriorated again one day after heparin cessation and then referred to our department.

Upon examination, His GCS was E1V_xM1 (endotracheal tube) and slow response to the light of both eyes. Vital signs T 35.4 ⁰C; HR 84 beats/min; RR 22 breaths/min on ventilator; BP 140/69 mmHg on vasoconstrictor epinephrine; O2 saturation, 90%

Laboratory test showed high increase of white blood cells (WBC) 53.09 10³/L, NLR 58.1; blood urea nitrogen (BUN) 47 mg/dL; creatinine 0.81 mg/dL. Coagulation function tests were APTT 20,2 seconds; PT 11.9 seconds; INR 1.11 and D-dimer 5,308 ng/mL (previous D-dimer was >50,000) and fibrinogen 525 mg/dL. Liver function and electrocardiogram were normal. Second Reverse transcription polymerase

chain reaction (RT-PCR) from a nasopharyngeal swab sample was negative for SARS-CoV-2 when he referred to us. The laboratory results are listed in the table 1.

Head Non-Contrast Computed Tomography (NCCT) showed hyperdensity at superior sagittal sinus (SSS), and right transverse sinuses (TS) suggesting a cerebral sinus venous thrombosis (CSVT) (Figure 2A, B, C). There were associated cerebral edema at left frontal, parietal lobe and cerebellum (Figure 2B). Thorax CT scan revealed ground glass opacity subpleural bilateral with fibrotic appearance in both lung and pulmonary angiography, thrombosis at segment 8 and 9 both lungs was found (Figure 2D). The pulmonary CT-angiography (CTA) results were pulmonary embolism and thrombosis of left and right pulmonary arteries. Due to massive thrombosis, we decided to give him Streptokinase intravenously and heparin. After 3 days of this treatment the patient became desaturated (SatO₂ 40%) with spontaneous pneumothorax and patient passed away on the next day

Table 1. Summary of laboratory findings at admission

Laboratory findings	Case 1	Case 2
White cell count (per mm ³)	14.1	53.03
Total neutrophils (per mm ³)	13.02	49.53
Total lymphocytes (per mm ³)	0.39	0.84
Neutrophil-Lymphocyte Ratio	33	59
Total monocytes (per mm ³)	0.58	1.35
Hemoglobin level (g/dL)	14.1	15.0
Hematocrite	40.4	44.3
Platelet count (per mm ³)	311	397
ESR	93	-
C-Reactive Protein (mg/L)	-	221.1 (before 391)
Procalcitonin (mg/L)	-	7.76
Lactate dehydrogenase (U/L)	-	600
Activated partial thromboplastin time (sec)	27.4	20.2
Prothrombin time (sec)	9.3	11.9
INR	0.90	1.11
D-dimer level (ng/mL)	21,176	5,308 (before >50.000)
Fibrinogen level (mg/dL)	446	525 (before 439)
Albumin level (g/dL)	2.71	-
SGOT (U/L)	29	169
SGPT (U/L)	24	238
Blood Urea Nitrogen (mg/dL)	14	31
Serum Creatinine (mg/dL)	0.74	0.52
Blood Glucose	254	130
HbA1C	6.5	-
Natrium (mg/dL)	133	139
Kalium (mg/dL)	3.0	4.5
Calcium (mg/dL)	7.4	7.6

Magnesium (mg/dL)	2.17	2.2
CKMB	-	31.8
Troponin I	-	0.61
Blood gas analysis:		
- pH	7.42	7.29
- pCO₂ (mmHg)	40	45
- pO₂ (mmHg)	136	92
- Base excess (mmol)	2	-4
- Lactate (mmol/L)	-	1.8

ESR= erythrocyte sedimentation rate ; INR= international normalized ratio; SGOT= serum glutamic oxaloacetic transaminase; SGPT= serum glutamic pyruvic transaminase; HbA1c= hemoglobin A1c; and CKMB= creatinine kinase myocardial band.

Discussion

We reported the two cases of cerebral venous thrombosis with two different onsets of neurological complications. The first patient had comorbidities of hypertension and diabetes mellitus. The later was without any comorbidities except old age (72 years-old). Patients with comorbidities are known have greater disease severity of COVID-19(13). In this case, the second case has poorer outcome. Cerebral venous thrombosis in this series are neurological manifestation of COVID-19. Both of patients had been confirmed being infected by SARS-CoV2 with respiratory symptoms as first presentation. The CSVT itself is rare condition in cerebrovascular disease for approximately 0.5% to 1% to all stroke cases (14–16), with multiple factors associated such as prior medical conditions (thrombophilia, inflammatory bowel disease), transient situations (pregnancy, dehydration, infection), selected medication (Oral contraceptives, substance abuse), and unpredictable events (Head trauma) (16) by which thrombus formation become more aggravated. In this case report, COVID-19 had caused proinflammatory and pro coagulation state to create CSVT.

CSVV is more common in young individuals with broad manifestation depends on the location of thrombosis(14,17). The difference in clinical presentation of both patient was determined by the location of CSVV and location brain edema. First patient showed better clinical presentation since It only involved supratentorial brain. The second patient showed worse clinical presentation and grave prognosis due to involvement of infratentorial brain edema. Head NCCT scan of the second case showed direct signs of dense triangle sign (Figure 2B white arrow) and cord sign at right TS (Figure 2C white arrow). CTV of the first patient showed filling defect at bilateral TS and SSS (Figure 1E, F white arrows). We choose CTV over MRI during COVID 19 since CTV is more rapid and also an accurate technique to detect cerebral venous

thrombosis (18). The massive thrombosis and emboli in the lungs were the consequences of patients with hypercoagulable and immobile condition, for 31% incidence of thrombotic complications in ICU patients with COVID-19 (19). He had late complications because of worse coagulation marker at first admission in hospital, also had been immobilized for 10 days.

The mortality in CSVT is 1% at discharge and continuing to decrease with the use of anticoagulant treatment(15). The poor outcome and prognosis of CSVT are associated with age more >37 years, male, coma, neurological deficits, encephalopathy, decreased level of consciousness, hemiparesis, and seizures (16). The main cause of early death after acute CSVT is trans-tentorial herniation secondary due to multiple lesions or to diffuse brain edema (16). Another causes are status epilepticus, medical complications, and pulmonary embolism (16). The second patients had pulmonary embolism and thrombosis at the same time, but other organ still in good condition from the laboratory results (Table 1).

Almost all patients with COVID-19 present with involvement of the lung such as cough, shortness of breath or acute respiratory distress syndrome (ARDS)(20). SARS-CoV-2 is transmitted primarily via respiratory droplet and infects the lung and the conjunctival mucosa as a portal of infection (21). The entry of SARS-CoV-2 into the human host cells rely on the surface angiotensin-converting enzyme 2 (ACE2) which is most expressed in the type II surfactant-secreting alveolar cells of the lungs(22). The incubation period is approximately 4-5 days before the onset of symptoms (20,23).

SARS-CoV-2 infection activates innate and adaptive immune response by rapid and well-coordinated immune response, excessive inflammatory innate response and dysregulated adaptive host immune defense(24). The hyperinflammation SARS-CoV-2 known as “cytokine storm” is being a major cause of disease severity and death confirmed by the higher levels of inflammatory markers in blood such as C-reactive protein, ferritin, and D-dimers (25,26). Severe COVID-19 are correlated with lymphocytopenia and increase total neutrophils (27). NEU can induce cell DNA damage and free the virus from the cell by releasing reactive oxygen species(28). Neutrophils (NEU) are leukocyte that activates and migrates from the venous system to the immune organ or system. Elevation NLR may predict the worse prognostic in COVID-19 patients(28). The NLR in both patients are high and the second case had larger NLR and ended with death.

The interleukin (IL)-1 β , IL-6, IL-12, interferon γ (IFN- γ), IFN- γ -inducible protein 10 (IP10) and monocyte chemoattractant protein (MCP) were associated with pulmonary inflammation and extensive lung damage in SARS patients(29). Both patients had severe pneumonia, seen with Thorax CT scan as GGO. Elderly patients are more susceptible to worsening due to immune system instability against viral infections due to decreased interferon production(30). The worse clinical experience in the second patient was most likely the result of this immunity instability. SARS-CoV-2 known to suppress the induction of antiviral type I interferon (IFN- α/β)(30). If we have modalities to counting the cytokines serum, we assumed that both patients had elevated cytokines mentioned before.

Clinically relevant hemostatic changes occurs 50-70% in septic patients, with 35% patients meet the criteria of disseminated intravascular coagulation(31). Patient with COVID-19 has diffused inflammation

that activates coagulation system. This system consumes clotting factor and resulting in DIC(32). The systemic inflammatory damages the endothelial cells and activates mononuclear cells to produce proinflammatory cytokines that promotes coagulation(33). These cells expressed proteins that initiate coagulation. Thrombin elicits the production of monocyte chemoattractant protein 1 and IL-6 in monocytes, fibroblasts, and mesothelial cells, and the production of IL-6 and IL-8 in vascular endothelial cells by interacting with protease-activated receptors (PARs)1,3, and 4(31). PARs are a transmembrane G-protein coupled receptors that has their own function from PAR1-4 (34). The PAR1,3,4 are receptors that are activated by thrombin. Via PAR2, factor Xa, and the issue factor-VIIa complex also upregulate IL-6 and IL-8 in vascular endothelial cells (31). The tissue factor VIIa catalyzes the conversion of factor X to Xa, which will form the prothrombinase complex with factor Va, prothrombin factor (II), and calcium, thereby generating thrombin (factor IIa)(32).The physiologic anticoagulant mechanisms and fibrinolysis are inhibited with by endothelial cells causes intravascular fibrin deposition (31).

Coagulation is controlled by three important physiological anticoagulant pathways: the antithrombin system, the activated protein C system and tissue factor inhibitor (TFPI). That three pathways are derange in sepsis that precipitated by cytokines(34). In sepsis, the high level of cytokines is found in the bloodstream. Hemostatic activation was mediated by TNF in sepsis. The expression of tissue factor in mononuclear cells and subsequent exposure to blood results in thrombin generation followed by fibrinogen to fibrin conversion. The platelet vessel wall interaction and activation of platelets contribute to microvascular clot formation(34).

The dysfunction of endothelial cell induced by COVID-19 results in thrombin generation and fibrinolysis shutdown(34). COVID-19 and hypercoagulability are implicating the pulmonary embolism (PE), vein thromboembolism (VTE), disseminated intravascular coagulation (DIC), and stroke(35). In critically ill patients may develop hypercoagulable state due to immobilization, mechanical ventilation, central venous access devices, and nutritional deficiencies(36). The second patient has more severe condition because he had been hospitalized with ventilator, central venous catheter, and immobilized for 10 days.

Hypercoagulability of SARS-CoV-2 manifesting as increase in D-dimer, LDH, fibrinogen, factor VIII (FVIII), von Willebrand factor (vWF), and decreased antithrombin(37). Patient with severe pneumonia especially ARDS has low oxygen concentration that increase the blood viscosity and inducing the hypoxia-inducible transcription factor-dependent signaling pathway (19). After the COVID-19 swab had been negative, the second patient was developed massive thrombosis. He had more D-dimer level than the first patient and length of treatment was longer, so the thrombosis process was still ongoing even though COVID-19 was negative and D-dimer level was decreased. It was a challenge to find out whether the second patient had previous thrombosis or not, therefore we take diagnostic approach in pulmonary embolism by checking D-dimer, while troponin I was used to check heart thrombosis(38). The second patient also had troponin I increased and normal ECG. We concluded this patient had brain, heart, and pulmonary thrombosis.

Anticoagulant that most commonly used to preventing DIC and VTE is low molecular weight heparin (LMWH) because it has anti-inflammatory effect(39). The first patient was given LMWH to minimize the contact with the patient. We checked again the D-dimer after 4 days and the D-dimer was decreased with improvement in neurological manifestation. The heparin intravenous is used to our second patient because he was in ICU and we can do close monitoring to the patient's APTT. Heparin interacts with many pro-inflammatory and procoagulant cascades to prevent inflammation and coagulopathy associated with sepsis (39). The use unfractionated heparin and LMWH are used in acute CSVT (9). The use of tissue-plasminogen activator (t-PA) fibrinolytic therapy were used in decompensated patients with no options for escalation of care(40). The second patient get fibrinolytic therapy the next day after the diagnosis CSVT. The response was not good, due to the condition going to be multiple organ failure on the third days of loss of consciousness.

Conclusion

CSVT is one of neurological complication and COVID -19 manifestation that can have grave prognosis, if this involves the brainstem venous drainage. Hypercoagulability is a complication of COVID-19 in patients with previous comorbid hypertension and diabetes mellitus. Thrombogenesis and coagulation cascades can be prolonged despite successful alteration to negative result of SARS-CoV2 rt-PCR test. Therefore, monitoring neutrophil to lymphocyte ration (NLR), D-dimer level, fibrinogen and CRP is paramount as well as indicators of poor prognosis. The use of heparin or LMWH may decrease the D-dimer but not increase the symptoms due to the complications.

List Of Abbreviations

ACE2	: angiotensin-converting enzyme 2
APTT	: Activated partial thromboplastin time
ARDS	: acute respiratory distress syndrome
BUN	: blood urea nitrogen
CKMB	: Creatinine Kinase Myocardial Band
COVID-19	: Coronavirus disease 2019
CRP	: C-Reactive Protein
CSVT	: cerebral sinus venous thrombosis
CT	: Computed Tomography
CTA	: CT angiography

CTV : CT venography

DIC : Disseminated Intravascular Coagulation

ESR : erythrocyte sedimentation rate

FVIII : factor VIII

GGO : Ground glass opacity

HbA1C : haemoglobin A1c

ICU : Intensive care unit

IFN : interferon

IL : interleukin

IP10 : inducible protein 10

INR : index normalized ratio

LDH : Lactate dehydrogenase

LMWH : low molecular weight heparin

MCP : monocyte chemoattractant protein

NEU : Neutrophils

NLR : neutrophil to lymphocyte

PAR : protease-activated receptors

PE : pulmonary embolism

PT : Prothrombin time

SARS-CoV2 : severe acute respiratory syndrome coronavirus 2

SGOT : Serum Glutamic Oxaloacetic Transaminase

SGPT : Serum Glutamic Pyruvic Transaminase

SSS : Superior sagittal sinus

TFPI : tissue factor inhibitor

t-PA	: tissue- plasminogen activator
TS	: Transverse sinus
VTE	: vein thromboembolism
vWF	: von Willebrand factor
WBC	: white blood cells

Declarations

Consent for publication: The Authors give consent for publication. Written informed consent was obtained from the legal guardian of the patients.

Competing interest: The Authors declare that they have no competing interest.

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Figures

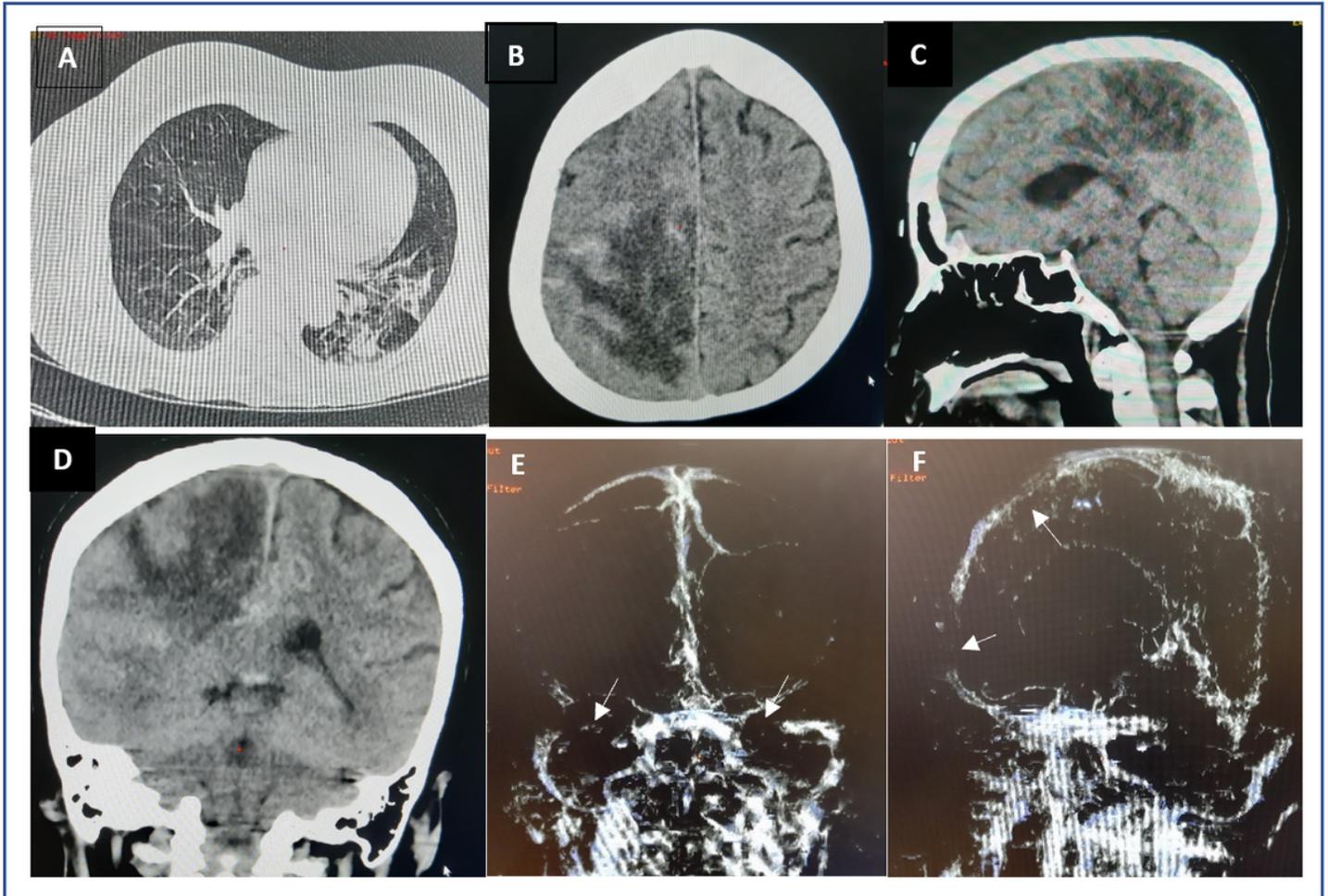


Figure 1

(A) Axial Thorax CT-scan showed ground glass opacity subpleural bilateral with fibrotic appearance in left lung. (B) Axial Head Non-Contrast CT-Scan (NCCT scan) showed parenchymal edema on right parietal lobe and hyperdense cortical veins. (C) Sagittal NCCT scan showed parenchymal edema on right parietal lobe and hyperdense superior sagittal sinus. (D) Coronal Head NCCT scan showed parenchymal edema on right parietal lobe and hyperdense superior sagittal sinus. (E, F) Brain CT Venography showed filling defect at SSS, TS bilateral, sigmoid sinus bilateral.

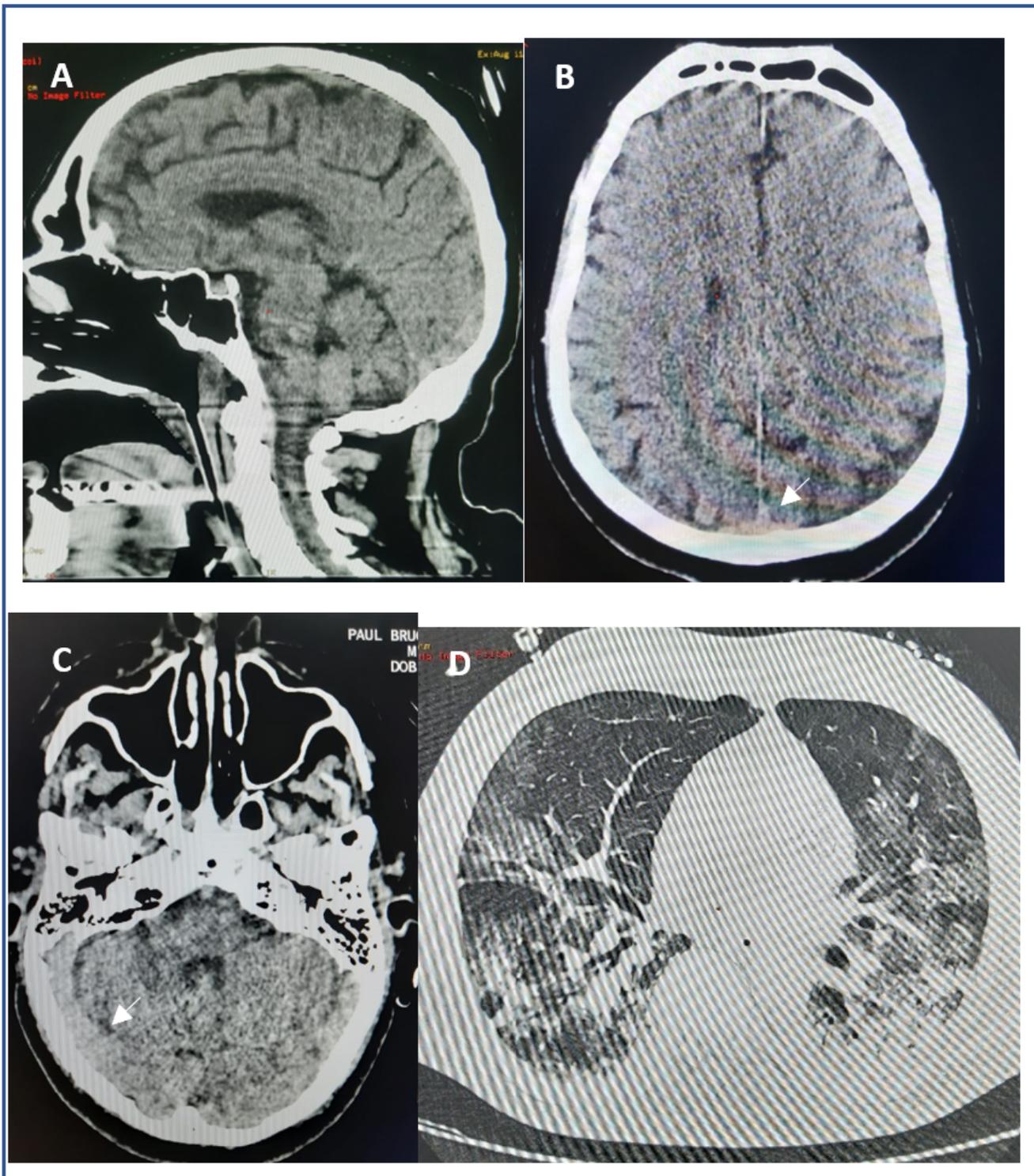


Figure 2

(A) Sagittal Head NCCT scan showed hyperdensity at superior sagittal sinus, and right transverse sinuses. (B) Axial Head NCCT scan showed hyperdensity at superior sagittal sinus (white arrow), and brain parenchymal edema on left parietal lobe. (C) Axial Head NCCT scan showed hyperdensity at right transverse sinus (white arrow). (D) Axial Thorax CT-scan showed ground glass opacity subpleural bilateral with fibrotic appearance in both lungs.