

Cerebrovascular complications in patients with SARS-CoV-2 infection: Case series

CURRENT STATUS: POSTED



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DOI:

10.21203/rs.3.rs-23137/v1

SUBJECT AREAS

Neurology

KEYWORDS

COVID-19, Coronavirus, SARS-CoV-2, Stroke, Neurological complications, Thromboembolic events

Abstract

Background: Italy is one of the most affected countries by the Coronavirus disease 2019 (COVID-19). The responsible pathogen is named Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2). The clinical spectrum ranges from asymptomatic infection to severe pneumonia leading to intensive care unit admission. Evidence of cerebrovascular complications associated with SARS-CoV-2 is limited. We herein report 6 patients who developed acute stroke during COVID-19 infection.

Methods: Retrospective case series of patients diagnosed with COVID-19 using reverse-transcriptase-polymerase-chain-reaction (RT-PCR) on nasopharyngeal swabs, who developed clinical and neuroimaging evidence of acute stroke during SARS-CoV-2 infection.

Results: Six patients were identified (5 men); median age was 69 years (range: 57-82). Stroke subtypes were ischemic (4, 67%) and hemorrhagic (2, 33%). All patients but 1 had pre-existing vascular risk factors. One patient developed encephalopathy prior to stroke, characterized by focal seizures and behavioral abnormalities. COVID-19-related pneumonia was severe (i.e. requiring critical care support) in 5/6 cases (83%). Liver enzyme alteration and lactate dehydrogenase (LDH) elevation was registered in all cases. Four patients (67%) manifested acute kidney failure prior to stroke. Four patients (67%) had abnormal coagulation tests. Outcome was poor in the majority of the patients: 4 died (67%), 1 is still in coma (20%) and the remaining 1 remains severely neurologically affected (mRS: 4).

Conclusions: Acute stroke can complicate the course of COVID-19 infection.

In our series, stroke developed mostly in patients with severe pneumonia and multi organ failure, liver enzymes and LDH were markedly increased in all cases, and the outcome was poor.

Introduction

Italy was the first country in Europe to witness an outbreak of the Coronavirus disease 2019 (COVID-19), which, as of April 6, has infected 1,277,196 people worldwide [1]. The responsible pathogen is named Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2). The clinical spectrum associated with COVID-19 ranges from asymptomatic infection to severe pneumonia leading to intensive care unit (ICU) admission [2-4]. Evidence of cerebrovascular complications associated with

SARS-CoV-2 is limited, but previous reports from the SARS epidemic in Asia in 2003 suggested a higher incidence of thromboembolic complications, including stroke [5]. Management of acute stroke in the setting of this pandemic disease poses unique challenges, including the need to maintain high quality stroke care with limited resources, while at the same time preventing infection spread to patients and physicians [6]. A better characterization of cerebrovascular complications associated with COVID-19 infection is important to guide decision making.

We herein report clinical spectrum, neuroimaging findings, and outcome of 6 patients developing acute stroke during COVID-19 infection.

Methods

This is a retrospective observational case series of patients developing clinical and neuroimaging evidence of acute stroke during COVID-19 infection. We included only patients with laboratory-confirmed COVID-19 infection who were admitted to the Fondazione Poliambulanza Hospital, Brescia, Italy or the Udine University Hospital, Udine, Italy, between March 16 and April 5, 2020. A confirmed case of COVID-19 was defined by a positive result on a reverse-transcriptase-polymerase-chain-reaction (RT-PCR) assay on nasopharyngeal swabs. Demographic data, information on clinical presentation and evolution, and laboratory and radiologic results were recorded. The severity of acute respiratory distress syndrome (ARDS) was rated using the $\text{PaO}_2/\text{FiO}_2$ ratio (partial pressure of arterial oxygen over the fraction of inspired oxygen) which was indicated whenever this data was available. Acute lung injury is present if $\text{PaO}_2/\text{FiO}_2$ ratio is ≤ 300 [7]. Each diagnosis of stroke was confirmed by brain computed tomography (CT)/CT angiography (CTA), and/or magnetic resonance imaging (MRI). All exams were reviewed by 2 experienced neuroradiologists (DB, MM). Neurological presentations were reviewed by 1 experienced neurologist (AV). Descriptive analysis is presented as frequencies and percentages for categorical variables and as the median and range for continuous variables. All procedures were performed in accordance with the institutional ethics committee and the Declaration of Helsinki.

Results

Six patients were identified (5 men); median age was 69 years (range: 57–82). Stroke subtypes were

ischemic (4, 67%) and hemorrhagic (2, 33%). All patients but 1 had pre-existing vascular risk factors. COVID-19-related pneumonia was severe (i.e. requiring critical care support) in 5/6 cases (83%). Liver enzyme alteration and lactate dehydrogenase elevation was registered in all cases (100%). Four patients (67%) manifested acute kidney failure prior to stroke. Four patients (67%) had abnormal coagulation tests. Cerebrovascular complications were multiple and bilateral in 4 cases (67%). Outcome was poor in the majority of the patients: 4 died (67%), 1 is still in coma (20%) and the remaining 1 remains severely neurologically affected (mRS: 4). Clinical and laboratory data for all patients are summarized in the table.

Case 1

A 64-year-old man presented with cough, fever, and dyspnea. He had a previous history of smoking and myocardial infarction. His treatment included dual antiplatelet therapy (aspirin and clopidogrel) and anti-hypertensive drugs. Chest x-ray demonstrated bilateral areas of consolidation. The respiratory function progressively worsened and he was intubated and mechanically ventilated. In the following days the patient developed kidney failure (creatinine 3.22 mg/dL, n.v. 0.72–1.18), increased indices of inflammation and hepatic injury (C-reactive protein [CRP] 175 mg/L, n.v. <5; lactate dehydrogenase [LDH] 1032 IU/L, n.v. 125–220; aspartate aminotransferase [AST] 152 IU/L, n.v. 4–40; gamma-glutamyltransferase [GGT] 1165 IU/L, n.v. 8–61; total bilirubin 6.64 mg/dL, n.v. 0.2–1) and neurological deterioration, with inability to arouse during sedation lightening. All these features together were suggestive for multi organ failure. Coagulation tests showed thrombocytopenia ($78 \times 10^3/\mu\text{L}$, n.v. 150–400), associated with increased international normalized ratio (INR 1.62, n.v. 0.80–1.20) and increased D-dimer (7744 ng/ml, n.v. 0–500). A total body CT demonstrated extensive bilateral consolidations and ground-glass opacities of the lungs with bilateral pleural effusion (figure 1, A) and a filling defect in the right pulmonary artery due to pulmonary embolism. A cuneiform hypodense area was also detected in the spleen (figure 1, B). Brain CT showed multiple hypodense lesions involving different cortical and subcortical regions of both cerebral hemispheres (figure 1, C and D). Clinical, laboratory and imaging findings were consistent with pulmonary thrombo-embolism associated with multiple ischemic lesions involving brain and spleen. Few days after CT examination

the patient died.

Case 2

A 75-year-old man with diabetes mellitus and arterial hypertension presented with cough and fever for 5 days. His treatment included metformin and anti-hypertensive drugs (enalapril and hydrochlorothiazide). Clinical and laboratory findings indicated mild respiratory distress ($\text{PaO}_2/\text{FiO}_2$ 347). Chest CT demonstrated bilateral ground-glass opacities (figure 1, E). In the following days the respiratory function worsened and the patient was found unconscious with severe hypoxemia (SO_2 76%) and left-sided hemiparesis. Brain CT and CTA showed cortico-subcortical hypodensity over the right cingulate gyrus (figure 1, F-G) with the occlusion of the right pericallosal artery (figure 1, H). The patient was transferred to ICU where he was intubated and mechanically ventilated. Blood tests were significant for increased CRP (46 mg/L, n.v. <5), creatinine (5 mg/dL), liver enzymes (alanine aminotransferase [ALT] 74 IU/L, n.v. < 60), LDH (979 IU/L, n.v. 125–220), and INR (INR 1.53, n.v. 0.80–1.20). Nine days after, the patient's neurological status further declined, with a Glasgow Coma Scale (GCS) of 3. New brain CT showed multiple, bilateral, supratentorial (right frontal and parietal, left perirolandic and bilateral occipital) and infra-tentorial (vermian, left cerebellar hemisphere) ischemic lesions. Chest CT showed extension of ground-glass opacities and consolidations (involving about 75% of the lung parenchyma). Electroencephalogram (EEG) demonstrated bilateral slowing of the background rhythm. At last follow-up, his neurological status was not improved.

Case 3

An 82-year-old man presented with cough, fever and dyspnea. He had a previous history of diabetes mellitus, hypertensive cardiomyopathy, aortic valve regurgitation, and previous transitory ischemic attack. His treatment included aspirin and telmisartan. In 2015, he underwent left carotid endarterectomy. Clinical and laboratory evaluation showed moderate respiratory distress ($\text{PaO}_2/\text{FiO}_2$ 198), increased creatinine (1.22 mg/dl, n.v. 0.72–1.18), CRP (181 mg/L, n.v. <5), and LDH (507 IU/L, n.v. 125–220). Coagulation tests were normal. Chest radiography demonstrated hazy ground-glass opacities involving the peripheral and basal regions of the lungs with no significant pleural effusion (figure 2, A). The next day, he developed left-sided hemiparesis. Brain CT examination showed a new

small hypodense area in the right thalamus of presumed ischemic origin (figure 2, B, initial imaging; C, with ischemic lesion). CT-angiography showed no intra-luminal filling defect in the carotid arteries, vertebrobasilar system and other intra-cranial vessels. During hospitalization, he was treated with dual antiplatelet therapy (aspirin and clopidogrel) together with enoxaparin. A new brain CT performed 2 days later showed appearance of an additional small hypodense area in the centrum semiovale (figure 2, D). No intra-axial hemorrhages were detected. The following day the patient rapidly became comatose and died.

Case 4

A 76-year-old woman presented with cough and fever for 10 days. The patient had a previous history of arterial hypertension, diabetes mellitus, aortic valve replacement, and cerebellar stroke. Her treatment included aspirin and warfarin. Clinical and laboratory evaluation indicated mild respiratory distress ($\text{PaO}_2/\text{FiO}_2$ 261). Chest CT demonstrated multiple areas of ground glass opacities and consolidations mainly involving the lower lobes (figure 2, E). Family members reported a number of episodes of transient loss of consciousness, followed by confusion, in the days preceding admission to the hospital. Blood tests showed increased CRP (12 mg/L, n.v. <5) and D-dimer (1381 ng/ml, n.v. 0–500). EEG showed a normal background in the alpha range (8 Hz), associated with recurrent sharp slow waves over the left temporal region, which occasionally were seen also on the right homologous regions. The episodes were interpreted as focal seizures and treatment with levetiracetam was introduced. A brain CT demonstrated a small hypodense area (5 mm) in the head of the right caudate nucleus referable to a lacunar infarction. The next day, a contrast-enhanced brain MRI showed a small rounded area of diffusion-restriction on the left pre-rolandic gyrus (figure 2, F: fluid attenuated inversion recovery [FLAIR] imaging; G: diffusion-weighted imaging [DWI]). The lesion previously noted in the right caudate nucleus was seen hyperintense on T2-FLAIR, with no diffusion restriction but faint contrast enhancement (figure 2, H). A small cortical-leptomeningeal area of enhancement was also noted in the left middle frontal gyrus at level of the superior frontal sulcus. T2* GRE revealed no hypointense lesions consistent with hemorrhagic lesions. Brain MRI angiography showed no alterations of intra-cranic vessels. In the following days, the patient remained confused and

demonstrated severe behavioral abnormalities, including aggressiveness. Cerebrospinal fluid analysis demonstrated normal protein content (0.5 g/L), 0 leukocyte, and normal IgG index. A comprehensive autoimmune screening was unrevealing. A new EEG excluded non-convulsive status epilepticus. At last follow-up, the patient was still hospitalized and severely neurologically affected (mRS = 4).

Case 5

A 57-year-old man presented fever and cough for a week with associated dyspnea for 3 days. He had a previous history of hypertension and thrombocytosis. Treatment included acetylsalicylic acid, hydroxyurea and ramipril. Clinical and laboratory evaluation showed moderate respiratory distress ($\text{PaO}_2/\text{FiO}_2$ 191). Chest CT demonstrated diffuse bilateral ground-glass opacities with no pleural effusion (figure 3, A). The respiratory function progressively worsened, and he was transferred to ICU for invasive ventilation. The patient received 4000 IU enoxaparin daily subcutaneously for the prevention of venous thromboembolic disease. During the following days he developed kidney failure (creatinine 3.24 mg/dL) treated with veno-venous hemofiltration (CVVH). Indices of inflammation and hepatic injury were increased (CRP 214 mg/L, n.v. <5; LDH 1013 U/L, n.v. 125–220; AST 97 U/L, n.v. <35; GGT 454 U/L, n.v. 8–61). Eleven days after the hospital admission the patient was found with bilaterally fixed and dilated pupils and a GCS of 3. Coagulation tests revealed prolonged aPTT (53.1 seconds, n.v. 23.5–35.0) and increased D-dimer (2866 ng/ml, n.v. 0–500). A brain CT demonstrated cerebellar hemorrhages (figure 3, B,C) in both cerebellar hemispheres (diameter of 4.8 cm on right, and 3.6 cm on the left) with compression of the fourth ventricle and the brainstem. Supratentorial hydrocephalus and diffuse obliteration of sulci were also noted (figure 3, D). CTA did not support the possibility of venous infarction due to non-opacification of the venous vessels. One hour after CT examination the patient died.

Case 6

A previously healthy 57-year-old man presented with cough and fever for 10 days with associated dyspnea for 4 days. Clinical and laboratory evaluation showed respiratory insufficiency ($\text{PaO}_2/\text{FiO}_2$ 197), increased CRP (21 mg/L, n.v. <5), and alteration of the hepatic function (LDH 771 U/L, n.v. 125–220; AST 100 U/L, n.v. 4–40; GGT 152 U/L, n.v. 8–61). Chest CT demonstrated diffuse bilateral ground-

glass opacities with no pleural effusion (figure 3, E). Five days after admission his respiratory function worsened and he was transferred to ICU for invasive ventilation. He was treated with 4000 IU enoxaparin daily subcutaneously. Despite regular cardiac activity and well-supported respiratory function, 7 days after admission in ICU his neurological conditions suddenly deteriorated. The patient was found with bilaterally fixed and dilated pupils, with a GCS of 3. A brain CT (figure 3, F-H) demonstrated diffuse cerebral edema with a large right frontal hemorrhage (6.0 x 5.2 cm on the axial plane) extending to the ventricular system. The ventricles were displaced across the midline. Four additional smaller intra-axial hemorrhages occurred in both hemispheres. Coagulation tests were normal. Shortly after CT examination the patient died.

Discussion

We report the clinical and neuroimaging features of 6 patients with severe SARS-CoV-2 infection who developed acute stroke, 4 ischemic and 2 hemorrhagic. At the time the cerebrovascular complications ensued, all but one patient needed critical care support and most of them had evidence of multi organ failure. Cerebrovascular complications were typically multiple and bilateral, and most of the patients were elderly male with comorbidities. Taken together, these factors could account for the poor outcome observed in this group. Given the fact that vascular risk factors were frequent in this cohort, the association between SARS-CoV-2 and stroke might be coincidental. Nevertheless, a body of epidemiological, clinical and experimental evidence suggests that patients with COVID-19 are at higher risk of thromboembolic complications, including neurovascular diseases, in the acute phase of infection. In particular, previous experiences from other Coronavirus-related diseases, the 2003 SARS epidemic and the 2012 Middle East Respiratory Syndrome (MERS), have highlighted stroke, pulmonary embolism and myocardial infarction as possible complications, especially in critically ill patients [5, 8]. Additionally, a recent report from Wuhan, China, showed that acute cerebrovascular disease is not uncommon in COVID-19, and it represents a negative prognostic factor. Among 221 infected patients, 11 (5%) developed ischemic stroke, 1 (0.5%) cerebral venous thrombosis, and 1 (0,5%) brain hemorrhage [9]. In agreement with the finding of the present study, it was also observed that cardiovascular risk factors were common, while the patients demonstrated increased biomarkers

of inflammatory response as well as a hypercoagulable state [9].

The relationship between acute infection and stroke is complex and it was demonstrated for many types of bacterial and viral infections. Importantly, an increased risk of stroke was documented after respiratory infections, including influenza, and the risk was highest within the first week [10]. Accordingly, measures to prevent viral illnesses (e.g. influenza vaccination) were shown to be protective for the development of cerebrovascular disease [11]. Intriguingly, the association between infection and stroke is also relevant for patients with preexistent risk factors. In this group, the vulnerability of atherosclerotic plaques to rupture appears to be increased in the presence of systemic inflammation and sepsis [10]. The mechanisms by which viral infections can trigger stroke are multiple and depend on the associated pathogen and host characteristics. For example, varicella zoster virus (VZV) is responsible for a distinctive vasculopathy involving both large and small arteries, which can result in ischemic infarction of the brain and spinal cord, as well as subarachnoid and cerebral hemorrhage [12]. At autopsy, the cerebral arteries showed disruption of the internal elastic lamina and multinucleated giant cells, while the presence of VZV DNA was demonstrated in the posterior cerebral and basilar arteries [13]. Similarly, human immunodeficiency virus (HIV) is a known cause of large vessel vasculopathy (mainly aneurysmal), that can also involve the brain [14]. A vasculitic-like mechanism can also apply in the context of COVID-19, since localized fibrinoid necrosis as well as infiltration of monocytes, lymphocytes, and plasma cells into vessel walls were demonstrated in 3 cases of the 2003 SARS disease [15]. Interestingly enough, another type of Coronavirus (New Haven CoV) was associated with the development of systemic vasculitis of childhood (Kawasaki disease) in a case-control study [16]. An alternative mechanism leading to stroke during the course of an infection is the presence of a pro-thrombotic state. Numerous reports have documented various coagulation abnormalities (in particular raised D-dimer, thrombocytopenia and isolated prolonged aPTT) in patients with SARS-CoV, nearly two decades ago [17, 18]. Chong et al. studied an autopsy series of 8 SARS patients and demonstrated the presence of pulmonary embolism in half of them, while 1 patient developed non-bacterial valvular vegetations associated with infarctions of the heart, kidneys, spleen, and occipital lobe [18]. Similarly, an underlying thrombophilic

state can also be also hypothesized in SARS-CoV-2 infection, as suggested by report of pulmonary embolism in patients from Wuhan [19] and in Patient 1 of the present series who also presented brain and spleen lesions suggestive for embolization.

We observed a marked elevation of a ubiquitous cell enzyme (LDH) in all patients of the present series. Elevated serum LDH is associated with numerous clinical conditions, including hemolysis, cancer, and sepsis [20]. In the setting of COVID-19, it is possible that the very high LDH levels reflect the underlying respiratory failure and systemic shock. Its role as a potential prognostic factor in COVID-19-associated stroke should be further investigated.

No patient with ischemic stroke was treated with thrombolysis or thrombectomy in the present series. This could be related to the fact that the patients were critically ill, and the detection of changes in neurological status is highly complex in ICU patients, where lightening of sedation and frequent neurological follow-up is needed. All these measures can be less prompt in the presence of restricted resources and limited medical personnel, as in a catastrophic medical emergency like COVID-19. Finally, one patient (Case 4) developed an encephalopathy, characterized by focal seizures, in association with behavioral abnormalities, which preceded stroke and complicated hospital stay. No clear structural, autoimmune, or metabolic etiology was found. Given the fact that cases of encephalitis and encephalopathy linked to COVID-19 were recently reported [21], we cannot exclude that it was due to direct neuro-invasion of SARS-CoV-2, although we are unable to prove this hypothesis.

In conclusion, acute stroke can complicate the course of COVID-19 infection.

In our series, stroke developed mostly in patients with severe pneumonia and multi organ failure, liver enzymes and lactate dehydrogenase were markedly increased in all cases, and the outcome was poor.

Declarations

Authors' contributions: Study concept and design: MM, DB, AV

Acquisition of data: MM, DB

Analysis and interpretation of data: MM, DB, MC, SDA, GG, CB, AV

Drafting of the manuscript: AV, MM, DB

Critical revision of the manuscript for important intellectual content: MM, DB, MC, SDA, GG, CB, AV

Study supervision: MM

All authors read and approved the final manuscript.

Study Funding: No targeted funding reported.

Data Access, Responsibility, and Analysis: The Corresponding Author had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Compliance with ethical standards: Conflicts of interest: None reported.

Ethical standards: All procedures were performed in accordance with the institutional ethics committee and the Declaration of Helsinki.

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Table

Table: Characteristics of patients with cerebrovascular complications of SARS-CoV-2 infection

Cas e n° (Age, sex)	Stroke type	Vascular risk factors	SARS-CoV-2 involvement	Kidney failure	Liver enzyme alteration	Increased LDH	Abnormal blood clotting tests	Outcome
1 (64, M)	Ischemic (thromboembolic)	Previous smoker, history of myocardial infarction	Severe	+	+	+	+ (aPTT, - INR, D-dimer, - platelet count)	Death
2 (75, M)	Ischemic (thromboembolic)	Arterial hypertension, diabetes mellitus	Severe	+	+	+	+ (INR)	Coma (GCS 3)
3 (82, M)	Ischemic	Arterial hypertension, diabetes mellitus, and previous TIA	Severe	+	+	+	No	Death
4 (76, F)	Ischemic	Arterial hypertension, diabetes mellitus, aortic valve replacement , previous stroke	Moderate	No	+	+	+ (D-dimer)	mRS= 4
5 (57, M)	Hemorrhagic	Arterial hypertension, thrombocytosis	Severe	+	+	+	+ (aPTT, D-dimer)	Death
6 (57, M)	Hemorrhagic	None	Severe	No	+	+	No	Death

Figures

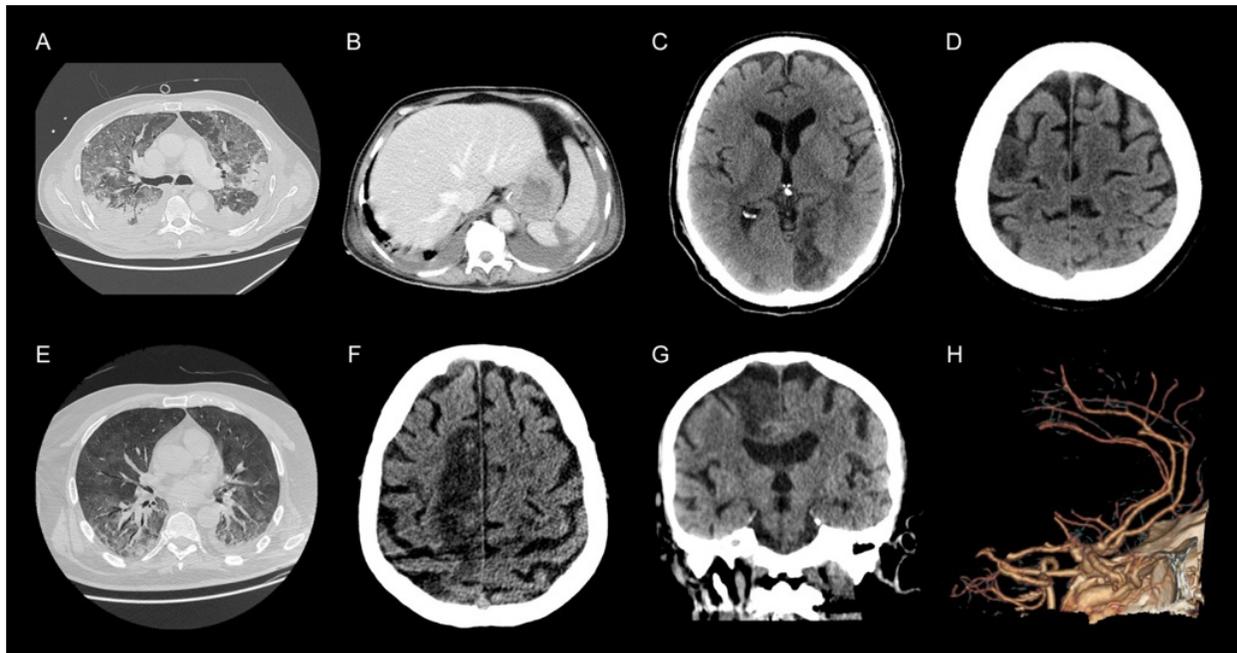


Figure 1

Total body and brain CT examination of Patient 1 (A-D) showing extensive bilateral consolidations and ground-glass opacities of the lungs (A), an hypodense area in the upper portion of the spleen (B) and two different ischemic lesions involving the left occipital lobe (C) and the right frontal precentral gyrus (D) respectively. Chest and brain CT examination of Patient 2 (E-H) showing bilateral consolidations and ground-glass opacities of the lungs with pleural effusion on the left side (E), an ischemic lesion involving the frontal lobe on the right side (F-G) and the occlusion of the right pericallosal artery on a 3D-Volume Rendering reconstruction of the brain CT angiography examination (H).

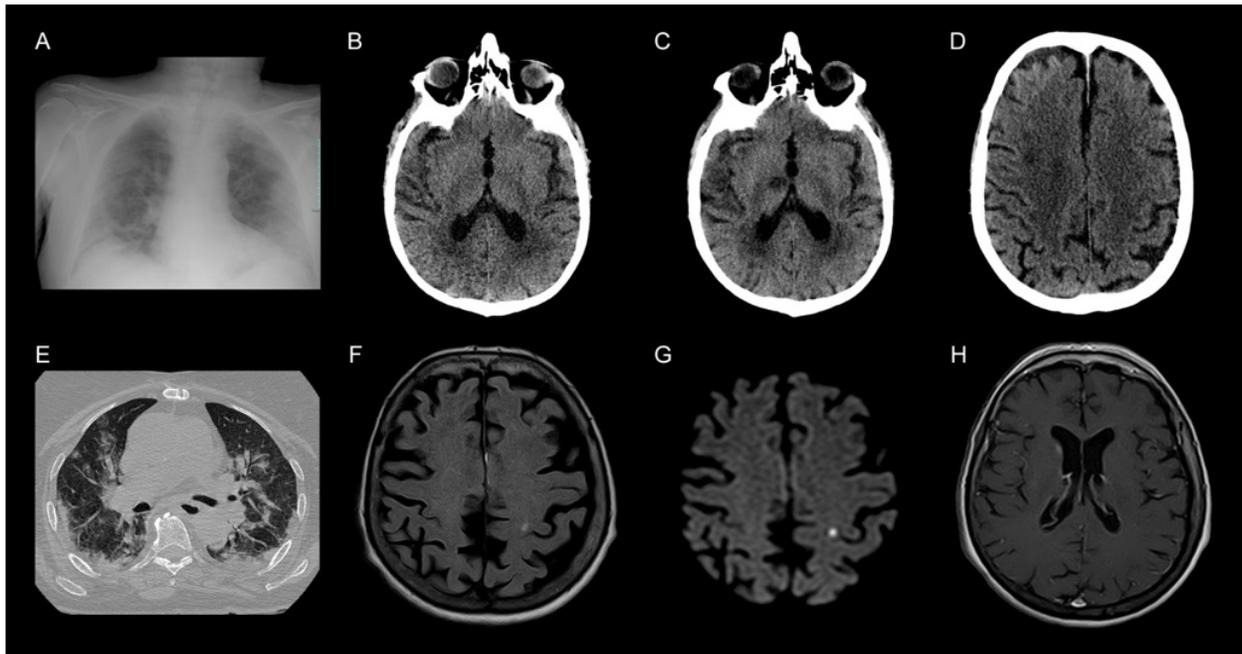


Figure 2

Chest X-Ray and two different brain CT examinations of Patient 3 (A-D) showing multiple opacities involving both lungs and a left lower lobe consolidation (A), the normal aspect of both thalami (B) and the appearance few days later of multiple ischemic lesions involving the right thalamus (C) and the subcortical white matter of the centrum semiovale of the same side (D). Chest CT and brain MRI examinations of Patient 4 (E-H) demonstrating multiple areas of ground glass opacities and consolidations mainly involving the lower lobes (E), a focal T2-FLAIR hyperintensity lesion in the left precentral gyrus (F) with a bright signal on DWI sequence (G) and mild post-contrast enhancement of the head of the right caudate nucleus (H).

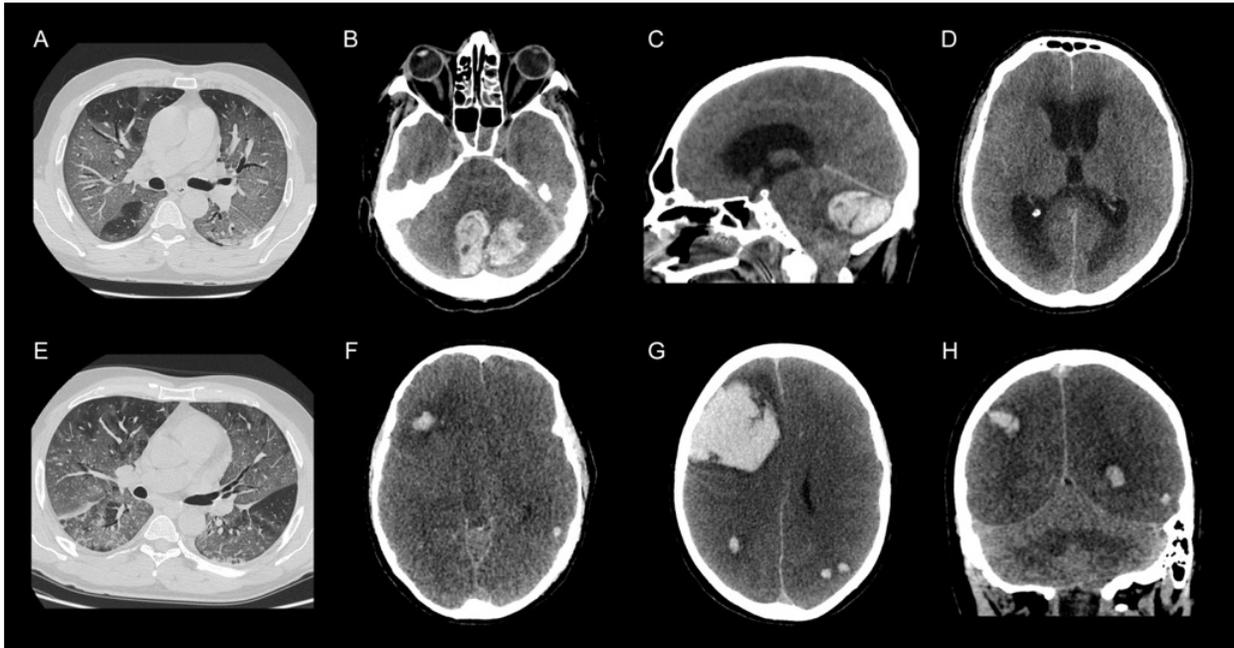


Figure 3

focal T2-FLAIR hyperintensity lesion in the left precentral gyrus (F) with a bright signal on DWI sequence (G) and mild post-contrast enhancement of the head of the right caudate nucleus (H). Figure 3 Chest and brain CT examination of Patient 5 (A-D) showing diffuse bilateral ground-glass opacities involving both lungs (A), a large cerebellar hemorrhage (B) which compresses the brainstem and the fourth ventricle determining a subsequent obstructive hydrocephalus (C-D). Chest and brain CT examination of Patient 6 (E-H) demonstrating diffuse bilateral ground-glass opacities with no pleural effusion (E), diffuse cerebral edema with loss of normal gray-white matter differentiation and obliteration of CSF spaces (F), a large right frontal hemorrhage in association with other smaller hemorrhages on the axial and on the coronal multiplanar reconstruction of brain CT (G-H) and a bright spot within the sagittal sinus suspected for dural sinus thrombosis.