CASE REPORT

COVID-19 related acute necrotizing encephalopathy presenting in the early postoperative period

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How to cite this article: Symeonidou E, Dimitriadou A, Morsi-Yeroyannis A, et al. COVID-19 related acute necrotizing encephalopathy presenting in the early postoperative period. Arch Clin Cases. 2023;10(2):78-85. doi: 10.22551/2023.39.1002.10246

ABSTRACT

Besides respiratory and gastrointestinal symptoms, SARS-CoV-2 also has potential neurotropic effects. Acute hemorrhagic necrotizing encephalopathy is a rare complication of Covid-19. This article presents a case of an 81-year-old female, fully vaccinated, who underwent laparoscopic transhiatal esophagectomy due to gastroesophageal junction cancer. In the early postoperative period, the patient developed persistent fever accompanied by acute quadriplegia, impaired consciousness, and no signs of respiratory distress. Imaging with Computed Tomography and Magnetic Resonance revealed multiple bilateral lesions both in gray and white matter, as well as pulmonary embolism. Covid-19 infection was added to the differential diagnosis three weeks later, after other possible causes were excluded. The molecular test obtained at that time for coronavirus was negative. However, the high clinical suspicion index led to Covid-19 antibody testing (IgG and IgA), which confirmed the diagnosis. The patient was treated with corticosteroids with noticeable clinical improvement. She was discharged to a rehabilitation center. Six months later, the patient was in good general condition, although a neurological deficit was still present. This case indicates the significance of a high clinical suspicion index, based on a combination of clinical manifestations and neuroimaging, and the confirmation of the diagnosis with molecular and antibody testing. Constant awareness of a possible Covid-19 infection among hospitalized patients is mandatory.

KEYWORDS: neuroimaging diagnosis; case report; acute hemorrhagic necrotizing encephalopathy; neurologic manifestations; covid-19; prompt treatment

INTRODUCTION

Covid-19 may affect many systems of the human body, including the central nervous system (CNS), causing a variety of symptoms and clinical conditions. Although SARS-CoV-2 appeared in 2019, some of the associated clinical manifestations are rare and not widely known among the medical community. In this article, we present a case of an 81-year-old female who underwent laparoscopic transhiatal esophagectomy, and on the 5th post-op day, she developed acute quadriplegia, aphasia, and an altered state of consciousness, accompanied by a persistent fever up to 38.3 degrees Celsius. Thorough imaging revealed acute necrotizing encephalopathy. Although the molecular test for Covid-19 was negative initially, the diagnosis was confirmed with IgA and IgG antibody testing. The aim of this article is to raise awareness regarding the rare, but severe neurological clinical manifestation of Covid-19, and the significance of regular testing of hospitalized patients, especially when they present a fever of unknown origin.

Received: April 2023; **Accepted after review:** May 2023; **Published:** June 2023.

CASE PRESENTATION

Preoperative Evaluation

An 81-year-old Caucasian female with gastroesophageal junction adenocarcinoma was admitted to our department for elective surgery (laparoscopic transhiatal esophagectomy). The malignancy was diagnosed eight months ago when the patient complained of epigastric pain. Gastroscopy revealed an ulcerative tumor in the lower esophagus expanding to the gastroesophageal junction. The patient received neoadjuvant chemotherapy. She was fully vaccinated for Covid 19 with two doses of Pfizer BioNTech, nine and six months earlier. Molecular (PCR) Covid-19 test one day before the admission was negative.

Her past medical history included diabetes mellitus type 2, hyperlipidemia, and osteoporosis. The patient did not have any allergies or prior surgeries, and she was a non-smoker.

Due to poor performance status, the patient underwent a laparoscopic transhiatal esophagectomy instead of an

Ivor-Lewis esophagectomy, with a cervical esophagogastric anastomosis. Epidural anesthesia was performed for pain management. The operation was uneventful but the patient was transferred to the Intensive Care Unit for monitoring, gradual awakening, and extubation. Perioperative antibiotic prophylaxis with ampicillin sulbactam was administered, as well as low molecular weight heparin.

Postoperative Course

On postoperative day (POD) 1, she was transferred to a general ward and the epidural bupivacaine was renewed. Although hemodynamically stable, she developed fever (38 degrees Celsius). On POD 2, she was commenced on total parenteral nutrition (TPN), and on POD 4 the antibiotic therapy was altered to piperacillin-tazobactam, as an empiric broad-spectrum antibiotic since the fever persisted and the source of the infection was unknown. The molecular Covid test on POD 4 was negative.

Neurologic Manifestations

On POD 5 she developed a sudden altered state of consciousness (Glasgow Coma Scale 9-10/15), tetraplegia, positive Babinski sign bilateral, and aphasia. Her vitals were stable; blood pressure 108/69 mm Hg, 96 beats per minute, 98% saturation rate, and temperature 37.1 degrees Celsius. Her laboratory results included white blood cells 15400 K/μL (normal range 3800-10500 K/μL), with 87.8% neutrophils (normal range 45-75%), hematocrit 30.9% (normal range 40-52%), c-reactive protein 111.8 mg/L (normal range <6 mg/L), sodium 133 mmol/L (normal range 136-145 mmol/L), and D-dimer level of 6167.9 μg/dL (normal range <500 μg/dL). After several hours, her temperature was 38.2 degrees Celsius.

Diagnostic Challenges and Treatment

Thorough imaging was performed. Magnetic Resonance Imaging (MRI) of the brain revealed multiple scattered white matter lesions in the bilateral frontal, temporal, and occipital cortices, corpus callosum, and the left cerebellum hemisphere. Lesions were characterized by a hyperintense signal in T2/FLAIR sequence, along with restricted diffusion, as shown in Figure 1. A Computed Tomography (CT) scan of the brain, cervix, and thorax combined with pulmonary angiogram protocol was performed right after, which besides the MRI brain findings, also demonstrated filling defects within branches of the pulmonary artery supplying the upper part of the right lower lobe, as well as the lingula on the left side, as shown in Figures 2 and 3. No signs of lower respiratory system infection were noticed.

After a neurological consult, the patient was initiated on levetiracetam 1000 mg twice a day, for primary prevention of seizures, atorvastatin 40 mg, and the low-molecular-weight heparin (LMWH) was modified to therapeutic dosage, enoxaparin 6000 IU every 12 hours. TPN and antibiotics were discontinued temporarily, and saline was enriched with a multivitamin infusion.

Disseminated intravascular coagulation (DIC) was excluded since schistocytes were absent. Thrombophilia testing was negative, antithrombin 77.3% (normal range 75-125%), Protein C 98% (normal range 70-140%), Protein S 64.4% (normal range 60.1-113.6%), all within normal range. Both blood and urine cultures on POD 4 were negative. However, the patient remained febrile every day since POD 4. Mild hyponatremia (sodium 132 mmol/L) was gradually corrected. TPN in combination with enteral feeding through a Levin catheter was provided since the patient was not able to swallow.

On the MRI performed a week later (Figure 4), the lesions with restricted diffusion were not visible. The rest of the findings remained similar.

The patient remained febrile, with a temperature reaching 38.2 degrees Celsius. The urine culture obtained on the 13th POD was positive for *Candida albicans*, whereas blood cultures remained negative. Micafungin was added to her medication.

On 20th post-op day, a significant drop in hematocrit level (23.6%) was noticed. Urgent CT of head, thorax and abdomen was performed, which revealed a large retroperitoneal hematoma, without signs of active contrast extravasation. The brain CT revealed decreased density of the lesions located in the white matter, surrounded by hyperintense lesions, indicating cortical necrosis. The patient was transfused with two units of red blood cells, and LMWH was changed to enoxaparin 4000 IU once daily, from 6000 IU every 12 hours. Her hematocrit remained stable after the transfusion and the hematoma was managed conservatively.

On 21st post-op day, both blood culture and central venous catheter tip culture were positive for *Candida parapsilosis*, and urine culture was positive for Pseudomonas aeruginosa, sensitive to meropenem, and the antibiotic course was modified. However, she remained febrile, reaching 38.2 degrees Celsius, despite the targeted antibiotic regime.

MRI of the brain was repeated on the 26th post-op day, which demonstrated new lesions in the frontal and parietal cortex, with hyperintense signal in T1 and hypointense in T2, indicating necrosis with signs of hemorrhage (Figures 5 and 6).

The unexplained neurological imaging in combination with the persistent fever, added Covid-19 to the differential diagnosis. Molecular (PCR) test for Covid-19 obtained on the 29th POD was negative. High clinical suspicion indicated antibody testing, which revealed SARS-CoV-2 IgG>80.000 AU/ml (normal range <50 AU/ml) and IgA>10 (positive >1,1). Treatment with corticosteroids was 1 gr methylprednisolone for a 24-hour infusion for 5 days, followed by 16 mg methylprednisolone oral three times a day, which was tapered gradually. The patient responded successfully to the treatment. She was at last afebrile after 33 days, and her neurological symptoms improved. She was able to talk and swallow, with persistent paraplegia and motor disability of the left arm.

Before discharge, both urine and blood cultures were negative. The histopathology report stated a low-grade adenocarcinoma of the gastroesophageal junction. The oncology board suggested that her general condition does not allow adjuvant treatment. She was transferred to a rehabilitation center for further physiotherapy sessions. After 6 months of follow-up, the patient was in good general condition and has shown specific improvement, especially regarding speech and upper-limb mobility, but still with residual neurologic deficits.

DISCUSSION

SARS-CoV-2, besides the pulmonary and gastrointestinal manifestations, which are the most common, also can develop neurologic complications. Up to 35% of Covid-19 patients will develop neurologic symptoms, more likely severe infection, apparently due to brain hypoxia [1]. A wide

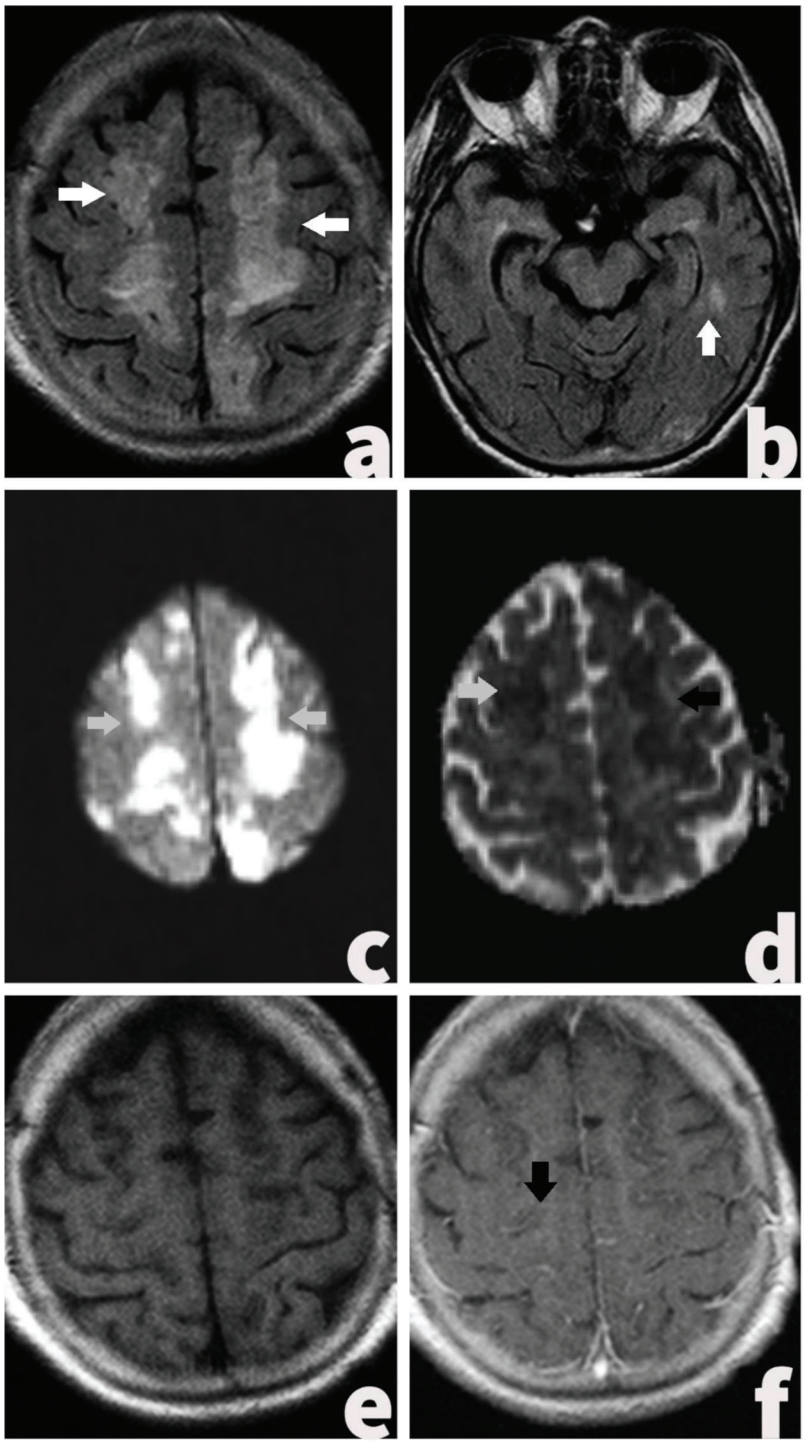

Fig. 1. Magnetic Resonance Imaging immediately after the acute onset of quadrivbplegia: a, b: T2/FLAIR sequence, axial view, multiple lesions of high MR signal located in white matter, more intense in bilateral frontal and parietal lobes, as well as in the left temporal and occipital cortex (white arrows), corpus callosum, and the left cerebellum. c, d: DWI/ADC map, axiall view: Lesions with restriction in diffusion sequences in bilateral frontal and left parietal lobes (grey arrows). e, f: T1 after intravenous administration of paramagnetic contrast. Abnormal enhancement of the meninges (black arrow).

range of Central Nervous System (CNS) complications has been associated with Covid-19, such as headache, impaired consciousness, delirium, hypogeusia/dysgeusia, hyposmia/anosmia, seizures, meningitis, encephalitis, myelitis, encephalopathy, and strokes [2]. According to a recent meta-analysis by Nazari et al. [3], the mortality rate of the patients with at least one CNS symptom was 10.47%, since the suppression of cardiopulmonary control centers might lead to acute respiratory failure. This fact indicates the importance of close monitoring of Covid-19 CNS symptoms.

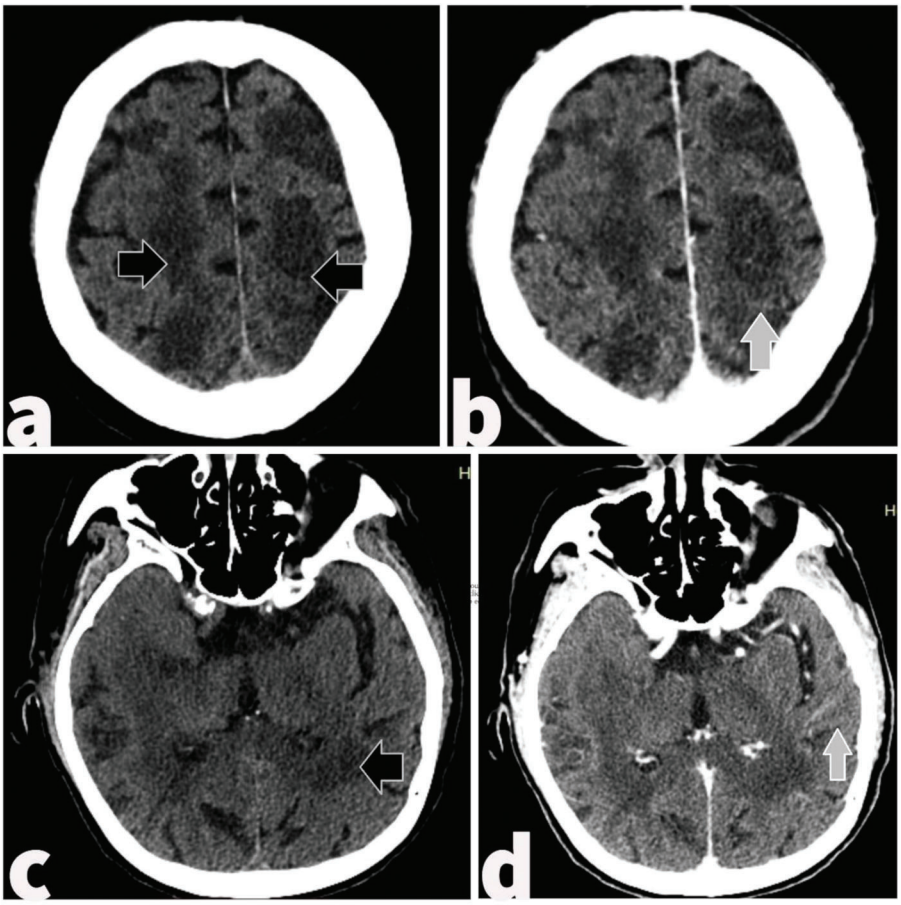

Fig. 2. Computed Tomography with intravenous contrast: Multiple hypodense areas in the frontal and parietal lobes (black arrows - a) and in the left temporal and occipital lobe (black arrows - c). Leptomeningeal enhancement is demonstrated (grey arrow – b and d).

Regarding the pathophysiology, SARS-CoV-2 may enter the CNS either through the hematogenous route, overcoming the blood-brain barrier, or through the peripheral nerve route with retrograde access [3]. After that, the virus infects nervous cells and endothelial cells through the angiotensin-converting enzyme 2 (ACE-2) host inhibitor, activating an inflammatory reaction with increased cytokine production, which results in irreversible neuronal damage. Destruction of the endothelium in cerebral capillaries, in combination with the hypercoagulable state also contributes to brain damage [4] and can accelerate blood clot formation, impairing the cerebral vasculature [3]. Hypoxia in combination with cytokines makes the blood-brain barrier even more permeable to the virus [3]. The coexistence of pulmonary embolism in our case supports the hypercoagulative hypothesis, whereas elevated C-reactive protein indicates an inflammatory reaction.

Acute Hemorrhagic Necrotic Encephalopathy (AHNE) is a rare neurodegenerative disease, triggered by a viral infection, which is characterized by multiple symmetrical necrotic lesions with signs of hemorrhage within the cerebellum, the thalami, and the brainstem. It has been most frequently associated with influenza infection in children [5]. The first case of Covid-19-related AHNE was reported by Poyiadji et al. [5]. Clinical manifestation involves changes in mental state, suppression of consciousness, delirium, coma, and convulsions. Neuroimaging with CT or MRI provides the diagnosis, whereas the virus is not detected in the cerebrospinal fluid (CSF). Microscopic examination confirms the endothelial damage to brain vessels [1]. Symmetric multifocal lesions with predominant bilateral thalamic and brainstem involvement are characteristic features. Cases with asymmetric multifocal lesions have also been reported and associated with better prognosis [6]. Brain stem, cerebral white and grey matter, and cerebellum might also be involved. MRI scan indicates increased signal intensity on T2/FLAIR and DWI with hemorrhage. A ring enhancement after contrast administration is another characteristic feature [7]. Therapy with methylprednisolone, 1g intravenously daily followed by prednisone taper, and antiseizure drugs has been recommended [1,6]. Immunotherapy and plasmapheresis have also been reported [7-9]. Because of the rare manifestation of this clinical entity, specific guidelines have not been established yet. However, this severe form of Covid-19 manifestation is accompanied by increased morbidity and mortality [8,10]. Our patient responded surprisingly well to corticosteroids treatment, although motor weakness in the legs and left arm remained.

Differential diagnosis includes Reversible Cerebral Vasoconstriction Syndrome (RCVS) caused by SARS-CoV-2. The downregulation of ACE-2 inhibitors leads to sympathetic and/or renin-angiotensin axis overactivity, resulting in blood

pressure spikes, and as a consequence, impaired cerebral autoregulation. This manifestation is usually associated with a good prognosis since 90-95% of the patients reach complete recovery [11]. The medical treatment involves aspirin and nimodipine.

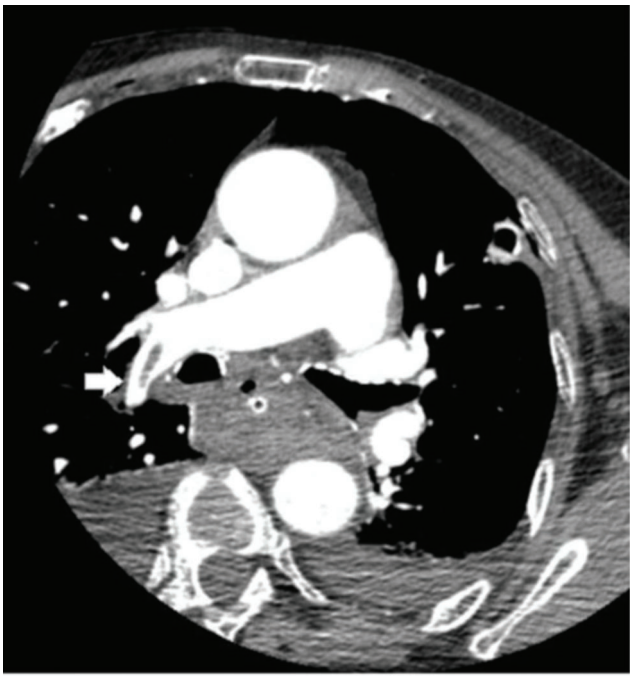

Fig. 3. Pulmonary embolism: Computed tomography image with pulmonary embolism protocol: filling defect (white arrow) within branches of the pulmonary artery supplying the upper part of the right lower lobe.

Another clinical condition that may be triggered by viral infections or vaccination is acute disseminated encephalomyelitis (ADEM), which is characterized by inflammatory demyelination of the central nervous system (CNS) [12]. It is more prevalent in children and young adults because of the higher frequency of vaccination and viral infections [13]. The first line of treatment is high-dose intravenous corticosteroids. Intravenous immunoglobulin is used for steroid-unresponsive patients or those who have contraindications for steroid administration, while plasmapheresis is reserved for fulminant cases [13].

PCR is the gold standard testing for the diagnosis of acute SARS-CoV-2 infection, but its sensitivity decreases gradually after the symptom onset, unlike serological testing, which increases in sensitivity over time [14]. Serological testing is very important for the diagnosis of suspected cases with negative molecular testing [15]. Most patients with SARS-CoV-2 infection seroconvert between 7 and 10 days after the exposure, with IgM and IgG antibodies being the most widely used biomarkers [15]. Secretory IgA plays an important role in protecting mucosal surfaces against pathogens, by neutralizing or preventing their attachment to epithelial cells. This way, IgA antibodies act as a first-line barrier against viral respiratory infections, providing an essential defensive mechanism [16]. Since SARS-CoV-2 targets the mucosa, IgA antibodies appear early in the disease course, and their levels correlate with the severity of the disease as shown by Zerfou et al. [17]. These results come in agreement with another study published by Cervia et al. [18] which supports the fact that serum IgA and IgG become positive 3 to 5 days after symptom onset in patients with severe Covid-19, especially ARDS. The severity of the neurologic manifestations in our case might explain the high levels of IgA and IgG antibodies. According to Sterlin et al. [16], SARS-CoV-2 neutralization is more closely correlated

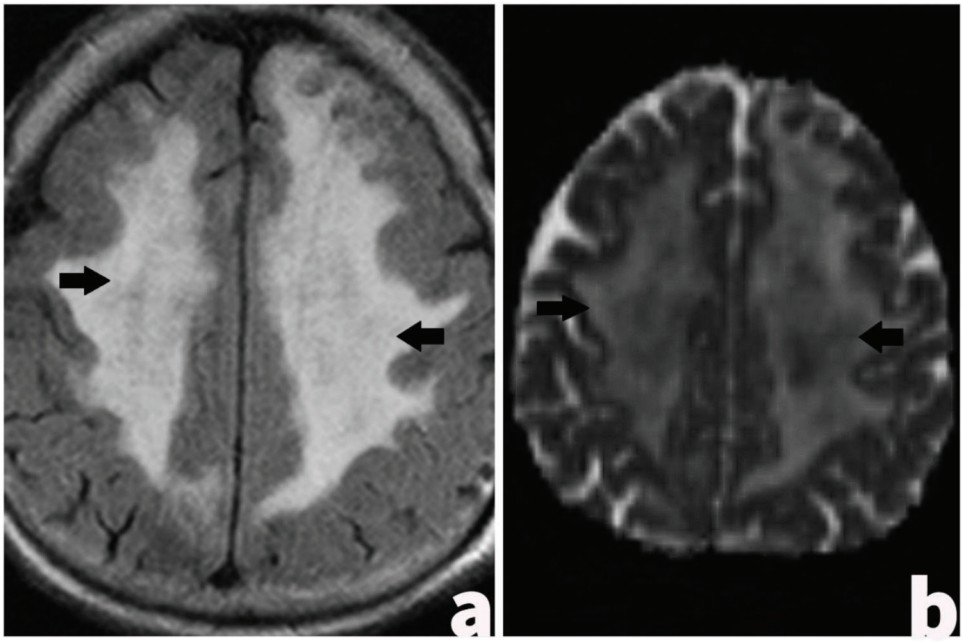

Fig. 4. Magnetic Resonance Imaging, without intravenous contrast, 7 days later: a: Fluid- attenuated Inversion Recovery (FLAIR) sequence and b: T2 sequence. Increased area of high signal intensity in the periventricular white matter, in comparison to previous MRI study.

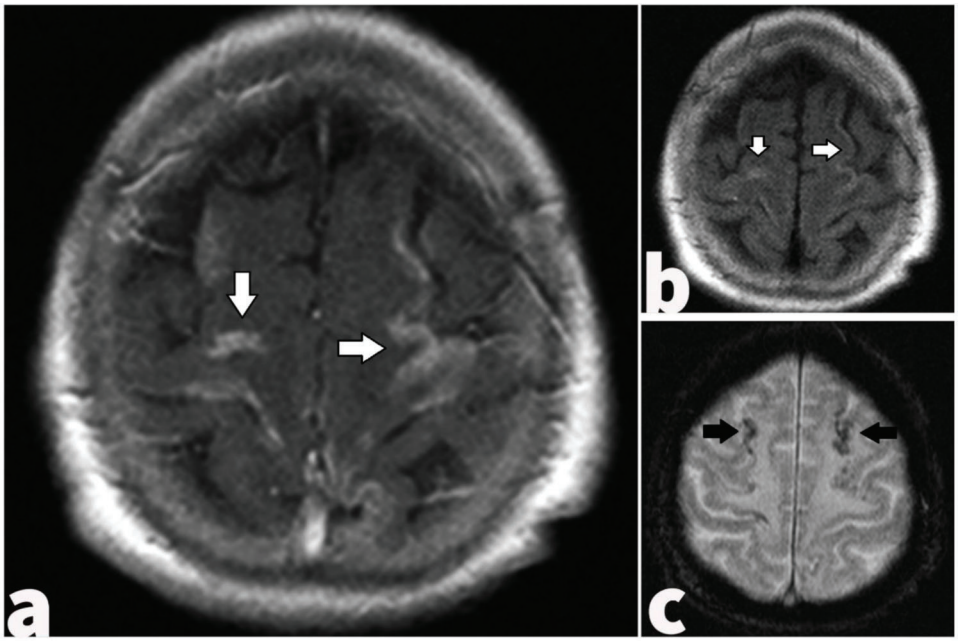

Fig. 5. Magnetic Resonance Imaging, 21 days later: a: T1 contrast images, b: T1W (weighted) and c: Susceptibility Weighted Imaging (SWI). Gyriform leptomeningeal enhancement (grey arrows-b), gyriform hyperintensities of the cortex (white arrows-a), and multiple hypointensities, cortical dot-like abnormalities (black arrows-c), indicating CNS infection with signs of recent hemorrhage.

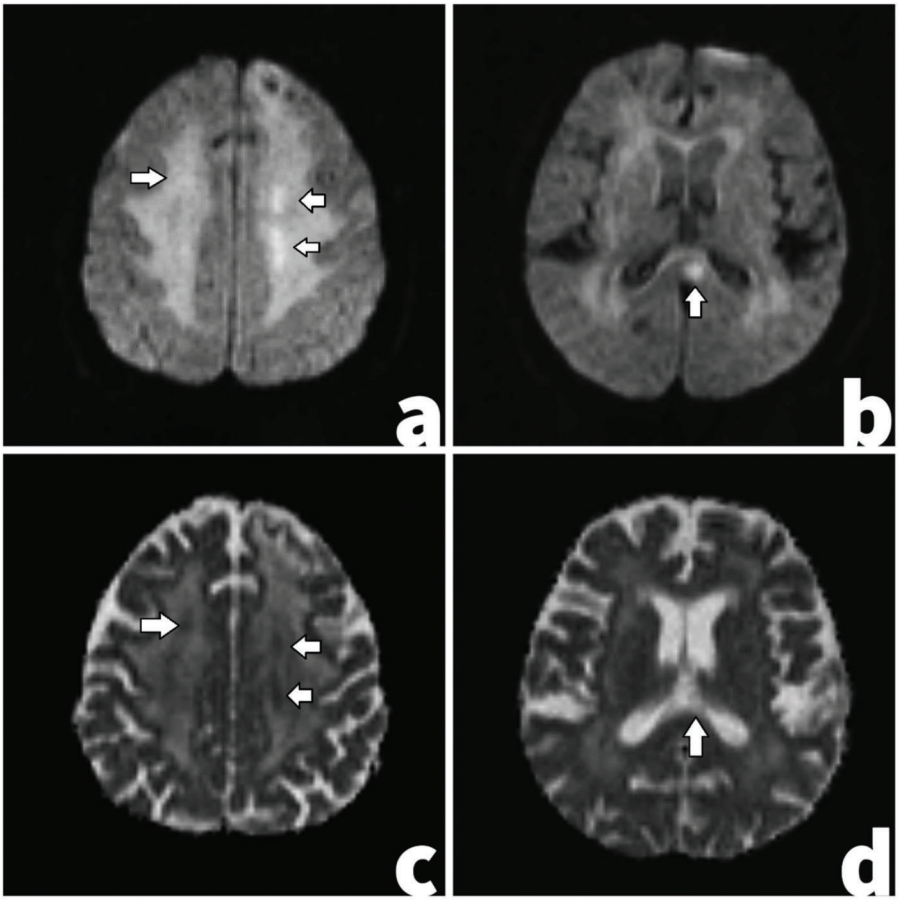

Fig. 6. Brain MRI 21 days later a: Diffusion Weighted Imaging (DWI), b: DWI, c: Apparent Diffusion Coefficient (ADC) map (same level as -a-) and d: ADC map (same level as -b-). Decrease of restriction of diffusion in centra semiovale (white arrows – a and c) and splenium (grey arrow – b and d) in comparison to previous MRI exams.

with IgA than IgM and IgG, highlighting the importance of IgA measurement in the early phase of Covid-19 in blood, saliva, or even BAL. Therefore, detecting IgM antibodies may not be necessary if IgA and IgG provide essential information for diagnosis [17]. However, in patients with low antigen exposure and mild symptoms, mucosal IgA may be detected in only about 15-20% of the cases [18], whereas serum IgA is usually absent. In addition, it is worth mentioning that vaccination, especially with mRNA vaccines, generally induces the expression of SARS-CoV-2 IgA antibodies [19], but their levels decrease quickly, whereas higher levels are observed in infected individuals [20]. In our case, the PCR tests acquired one day before and three weeks after the acute neurologic manifestation were negative. The patient received the second dose of BioNTech six months before the admission. However, IgA antibodies were ten times above normal limits. The persistent fever, indicating an active infection, in combination with the high clinical suspicion index raised by the neuroimaging and the high levels of IgA antibodies, established the diagnosis. Lumbar puncture was not performed because the patient was on therapeutic heparin dosage. A limitation of the current article is that more molecular tests (PCR) should have been obtained.

This case is unique due to the unconventional diagnostic algorithm that was followed. There is no evidence in the literature that this type of surgery may cause such a neurologic manifestation. The possibility of a COVID-19 infection was added to the list of differential diagnoses three weeks after the onset of the neurological symptoms, only after other possible explanations had been excluded. Initially, COVID-19 infection was not suspected since the patient had tested negative on a molecular test when admitted for elective surgery, and there were no signs of active pulmonary infection. However, when clinical suspicion was raised and molecular test was negative, the diagnosis was confirmed through serology test that detected IgA and IgG antibodies, which later matched the neuroimaging findings.

CONCLUSIONS

Acute hemorrhagic necrotizing encephalopathy represents a rare clinical manifestation of Covid-19. Early detection and prompt treatment of AHNE in Covid-19 patients can potentially improve clinical outcomes, especially considering its association with severe infection. The characteristic neuroimaging and the thorough laboratory testing, which includes molecular and serology testing for SARS-CoV-2, brain CT and MRI, are essential to set the diagnosis. Altered consciousness, fever, and signs of pulmonary embolism should raise high index of suspicion for AHNE in the context of Covid-19. It is also important to continually test hospitalized patients with fever of unknown origin for COVID-19, in order to prevent delayed diagnosis and treatment, and contribute to improved patient outcomes.

Acknowledgments
There are no conflicts of interest to declare.

Informed Consent
Written informed consent was obtained from the patient for publication of this case report. A copy of this consent is available for review by the Editor-in-Chief of this journal.

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