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Rapidly Fatal COVID-19-associated Acute Necrotizing Encephalopathy in a Previously Healthy 26-year-old Man

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Case Presentation

A 26-year-old man presented to our Emergency Department at 0200 on the day of admission with chief complaints of subjective fever, leg myalgias, and progressive dyspnea of one week duration. An oropharyngeal swab PCR had revealed SARS-CoV-2 RNA three days previously. He had not received a SARS CoV-2 vaccination, but had made an appointment to receive it just a few days prior to the onset of his symptoms.

The patient had no significant past medical history, was taking no medications except for ibuprofen and acetaminophen over the past week, and did not take recreational drugs. He specifically denied headache and had no prior history of seizure.

On admission, his HR was 150 bpm (sinus), RR 22, BP 105/46 mmHg, temp 40.2° C. and SpO_2 92% on room air. He was ill-appearing, but alert and oriented, his neck was supple and lung auscultation revealed bilateral rhonchi, but physical examination was otherwise unremarkable.

A CBC showed WBC 17.3 10^3/uL, hemoglobin 13.9 g/dl, and platelet count 168 K/uL. A complete metabolic profile was normal except for the following: Na 135 mmol/L, creatinine 1.7 mg/dL, AST 95 and ALT 134 IU/L. D-dimer was 1.08 ug/ml (normal range 0.00-0.50 ug/ml), and ferritin 783 ng/ml. A urine drug screen was negative. Chest radiography showed subtle bilateral pulmonary infiltrates. CT angiography of the chest was negative for pulmonary embolism but showed bilateral patchy infiltrates consistent with COVID19 pneumonia. One liter NS bolus and dexamethasone 10 mg were given intravenously, acetaminophen administered orally, and the patient was admitted to telemetry.

Shortly thereafter, the patient experienced a brief generalized seizure associated with urinary incontinence. He was stuporous post-ictally, exhibiting only arm flexion to painful stimuli. A stroke alert was called and radiographic studies emergently obtained. CT of the brain was normal and CT angiography of the head and neck showed no large vessel occlusion or flow-limiting stenosis, and a CT perfusion study (Figure 1) showed patchy Tmax prolongation in the right cerebellum and bilateral parietal occipital lobes "which may reflect artifact or relative ischemia" with no matching core infarct.

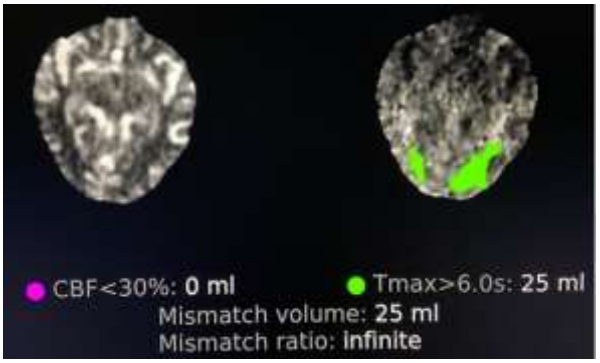

Figure 1. CT perfusion study showing mild bilateral posterior distribution ischemia (Tmax > 6 secs) without matching core infarct (CBF<30%), interpreted by a neuroradiologist as possible artifact.

The patient was transferred to the ICU at 10:00, and experienced a 40-second generalized tonic-clonic seizure shortly thereafter. Lorazepam 2mg was administered intravenously. The HR was 104, RR 21, BP 105/61, temp 36.5 C. and SpO_2 96% on 2L /min nasal canula oxygen. On neurological examination, the Glasgow Coma Scale was 3, right pupil was 3mm, left pupil 2mm - both reactive, the gaze was disconjugate and directed downward, there was no blink to visual threat, and glabellar ridge pressure did not elicit grimace, but minimal arm flexion. The gag reflex was positive. Peripheral reflexes were 2+ with down-going toes bilaterally. Levetiracetam 1000 mg bolus was administered intravenously. Glucose was 147 mg/dL. An EEG obtained at 12:00 showed diffuse bilateral slowing without seizure activity. A presumptive diagnosis of post-ictal encephalopathy was made. The patient seemed to be protecting his airway and nasal canula oxygen was continued.

The patient's condition was not noted to significantly change over the next 12 hours. There were no episodes of hypoxia, hypotension or hypoglycemia. Around 0100 on the second day of hospitalization, the patient exhibited extensor-posturing and appeared to be choking on his oral secretions. HR rose to 135, BP 155/99, RR 12 and temp 37.8 C. His SpO_2 fell into the mid 80% range. He no longer had a gag or cough reflex and he was emergently intubated without complication. MRI (Figure 2) and MRV of the brain were emergently obtained.

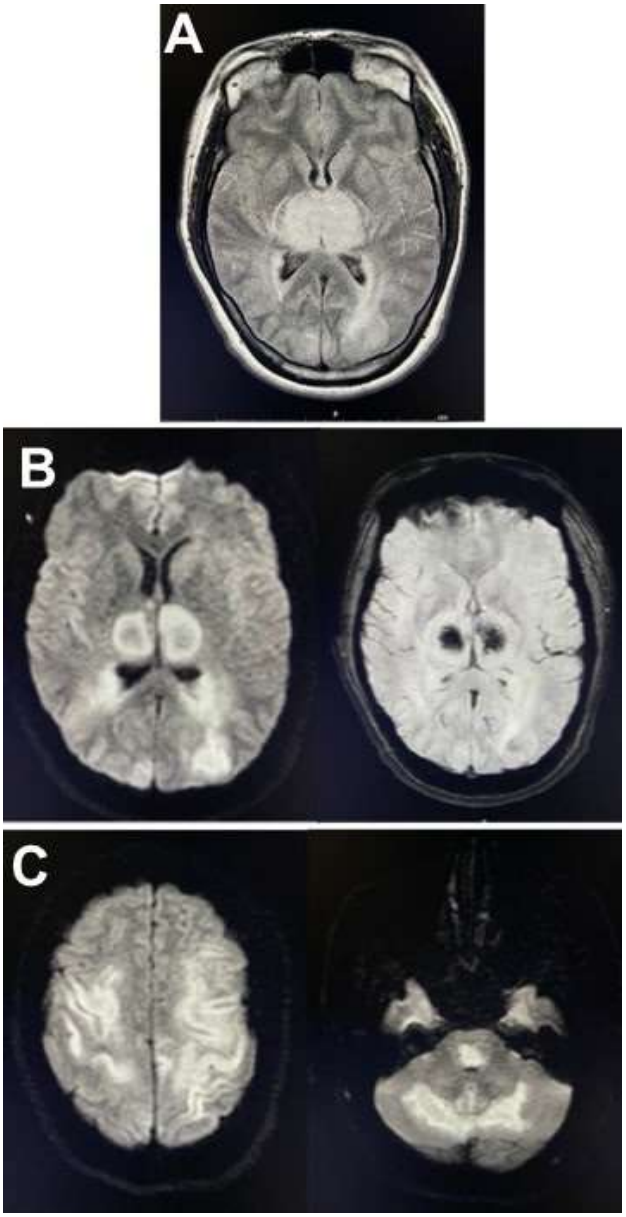

Figure 2. A: T2-weighted image demonstrating bilateral thalamic and L occipital white matter hypoattenuation. B: DWI and GRE images showing bilateral thalamic infarctions with hemorrhage. C: Representative DWI images of cerebrum and cerebellum and pons showing widespread diffusion restriction.

The MRI showed extensive diffusion restriction involving bilateral thalami, cerebellar hemispheres, pons, and cerebral hemispheres

with scattered hemorrhage most obvious/confluent in the bilateral thalami.

Normal flow voids were present in intracranial arteries and venous structures. Partial effacement of the lateral and third ventricles was noted, with early uncal herniation. The MRV showed no evidence of dural venous sinus thrombosis.

At 05:00 of the second hospital day, it was noted that the patient's pupils were dilated and unreactive and his respiratory rate was 16 – equal to the respiratory rate set on the ventilator. BP fell to 85/45 and norepinephrine infusion was started to maintain MAP >65 mmHg. STAT CT brain (Figure 3) showed hemorrhagic infarcts of the bilateral thalami with surrounding edema, interval development of low attenuation of the bilateral cerebrum and cerebellum, and mass effect with total effacement of fourth ventricle, basal cisterns and cerebral sulci consistent with severe cerebral edema.

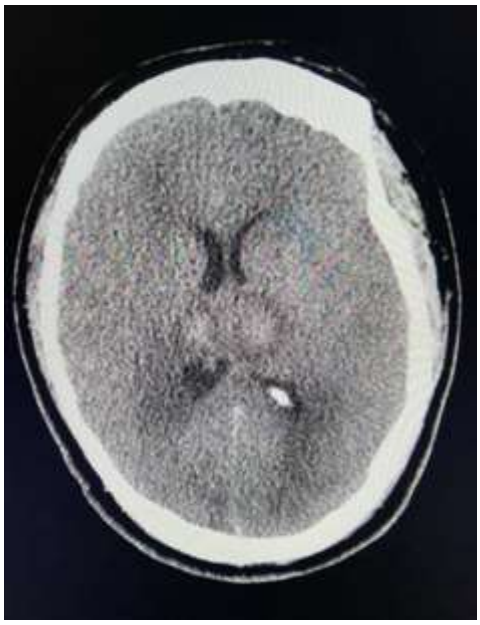

Figure 3. STAT CT brain from 05:30 on the second hospital day showing bilateral thalamic infarctions and diffuse cerebral edema with effacement of the sulci and loss of grey/white differentiation.

Two neurologists confirmed the clinical diagnosis of brain death, including an apnea test. A venous ammonia level ordered that morning was not drawn. An autopsy was requested by the physicians, but not able to be obtained.

Discussion

Acute necrotizing encephalopathy (ANE) is a rarely reported clinical-radiographic syndrome lacking pathopneumonic laboratory test or histological findings (1-3). It is characterized by an acute febrile viral prodrome, most commonly due to influenza or HHV-6, followed by rapidly progressive altered mental status and seizures. The most specific finding of ANE is necrosis of the bilateral thalami, appearing on MRI as hypoattenuated lesions on T2 and FLAIR images with diffusion restriction on DWI, and often with hemorrhage demonstrated on GRE images (as shown in figure 2 above). Symmetric multifocal lesions are typically seen throughout various other locations in the brain including the cerebral periventricular white matter, cerebellum, brainstem and spinal cord. Mizuguchi (who first described ANE in 1995) proposed elevation of serum aminotransferase without hyperammonemia, and cerebrospinal albuminocytologic dissociation (elevated CSF protein without leukocytosis) as laboratory criteria supporting the diagnosis of ANE (1,2). These were only partially evaluated in our patient. The mortality of ANE is 30% and significant neurological sequelae are common in survivors (2).

The clinical, radiographic and laboratory findings in our case are all characteristic of ANE, but our work-up was abbreviated by the patient's fulminant presentation. The differential diagnosis includes hyper-acute forms of acute disseminated encephalomyelitis (ADEM) or acute hemorrhagic leukoencephalitis that may also occur after a viral prodrome and may be associated with diffuse white matter lesions (4,5), although bilateral thalamic necrosis is not characteristic of either of these entities. Examination of cerebral spinal fluid (CSF) for pleocytosis, oligoclonal bands, and testing for

the myelin oligodendrocyte glycoprotein IgG autoantibody and the aquaporin-4 IgG serum autoantibody would have been indicated to further evaluate for the initial presentation of a relapsing CNS demyelinating disease (5,6). CSF examination would also have been helpful in ruling out viral encephalitis affecting the thalami, such as that caused by West Nile Virus (WNV) (7). An acute metabolic encephalopathy with diffuse brain edema, such as that caused by severe hyperammonemia associated with late-onset ornithine transcarbamylase deficiency (8) was not ruled out. Arterial or venous thromboembolism associated with COVID-19 were effectively ruled out by CT angiogram, CT perfusion and MRI and MRV findings.

We found five previous case reports of ANE as a complication of COVID-19, ranging 33-59 years of age (9-13). The onset of altered mental status occurred 3, 4, 7,10 and 21 days after onset of COVID-19 symptoms and rapidly progressed to coma. Two had generalized seizures, one myoclonus and another "rhythmic movements" of an upper extremity. All had bilateral hypoattenuation of the thalami on CT and MRI with variable involvement of temporal lobes, subinsular regions, cerebellum, brainstem and supratentorial grey and white matter. Two patients had EEGs that showed generalized slow waves. All underwent examination of CSF with negative PCR tests for various common encephalopathy viruses including herpes simplex virus 1&2 and WNV - four reported CSF protein and cell counts, three of which demonstrated albuminocytologic dissociation. Three patients received IVIG. Two patients died on days 5 and 8 after onset of neurological symptoms. Two recovered after prolonged ICU care and the outcome of the third patient was not reported. ANE may be less rare than these few case reports suggest. A retrospective study carried out at 11 hospitals in Europe describes radiographic findings of 64 COVID-19 patients with neurological symptoms (14). The most common finding was ischemic stroke, but 8 patients had MRI findings consistent with encephalitis and two had findings characteristic of ANE.

The pathogenesis of ANE is unknown. Ten cases of fatal ANE with brain biopsy are reported (1,15-19). These showed diffuse cerebral edema, and hemorrhagic necrosis invariably involving the thalami. An exudative small vessel vasculopathy with endothelial necrosis was found in 7/10 patients (This could perhaps explain the early CT perfusion findings interpreted as artifactual in our patient). Demyelination or inflammatory infiltration of the brain or leptomeninges was absent. There has been conjecture that these pathological findings might be due to disruption of the blood brain barrier caused by hypercytokinemia but there is scant supportive evidence (20).

There is no proven treatment for ANE. Corticosteroids, IVIg and plasma exchange have been previously used (3,9-11,21). Clinical trials are unlikely given the rarity of the disorder.

It was unfortunate that this young man had not availed himself of SARS CoV-2 vaccination. We did not make a pre-mortem diagnosis of ANE between his first abnormal CT brain at 0100 and his death at 06:00. We would have performed an LP, measured serum ammonia and given a trial of corticosteroids and IVIg if we had had more time.

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