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CASE REPORT

COVID-19-associated necrotizing encephalopathy presenting without active respiratory symptoms: a case report with histopathology

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Abstract
Acute necrotizing encephalopathy (ANE) is a rare complication of coronavirus disease 2019 (COVID-19) secondary to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. The condition is typically diagnosed based on characteristic neuroimaging findings in the context of active viral respiratory symptoms. We present a rare case of COVID-19-associated ANE presenting with expressive aphasia and encephalopathy in the absence of active respiratory symptoms. Initial evaluation revealed bilateral thalamic lesions and a mild neutrophilic-predominant pleocytosis on cerebrospinal fluid analysis, the latter of which has not been described in previously published cases. Presence of these atypical features prompted extensive diagnostic evaluation. Metagenomic next-generation sequencing on cerebrospinal fluid did not detect the presence of pathogenic nucleic acids. Thalamic biopsy revealed perivascular neutrophilic inflammation suggestive of small vessel vasculitis with surrounding hemorrhage and necrosis. Ultimately, the diagnosis was made following detection of SARS-CoV-2 serologies and after exclusion of alternative etiologies. The patient was successfully treated with a short course of high-dose methylprednisolone with favorable outcome.

Keywords SARS-CoV-2 · COVID-19 · MRI · Next-generation sequencing · Histopathology

Case report

A 48-year-old woman with hypertension was presented with acute onset expressive aphasia and encephalopathy. The patient was unable to provide a history, and the patient's husband denied any recent febrile illnesses or changes in overall health. The patient was afebrile (36.7 °C) and hypertensive (blood pressure 183/125 mmHg) without respiratory distress. Neurologically, she was alert but encephalopathic with an expressive, non-fluent aphasia and partial upward gaze palsy. An exam was otherwise non-focal.

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Chest x-ray showed retrocardiac atelectasis, but the lungs were otherwise clear. Blood work was notable for neutrophilic predominant leukocytosis without lymphopenia (14.0 K/mm3), microcytic anemia (9.1 g/dL), elevated erythrocyte sedimentation rate, and C-reactive protein (93 mm/h, 3.7 mg/dL). Head CT showed bilateral thalamic hypodensities (Fig. 1) with corresponding focal hypoattenuation on CT perfusion. Brain MRI demonstrated bilateral thalamic T2/fluid-attenuated inversion recovery (FLAIR) hyperintensities with rim enhancement and internal blooming artifact (Fig. 1). Nasopharyngeal swab for SARS-CoV-2 PCR was positive; repeat testing (day 2) was negative. Qualitative serologic assays for SARS-CoV-2 total and IgG antibodies were positive.

A broad differential was considered including arbovirus-related encephalitis, high-grade neoplasm, and COVID-19-associated acute necrotizing encephalopathy (ANE). CSF analysis showed a mild pleocytosis (cell count 14/mm3, 91% neutrophils), elevated protein (54 mg/dL), and normal glucose (73 mg/dL). Extensive evaluation for infectious, autoimmune, and neoplastic etiologies was unrevealing.

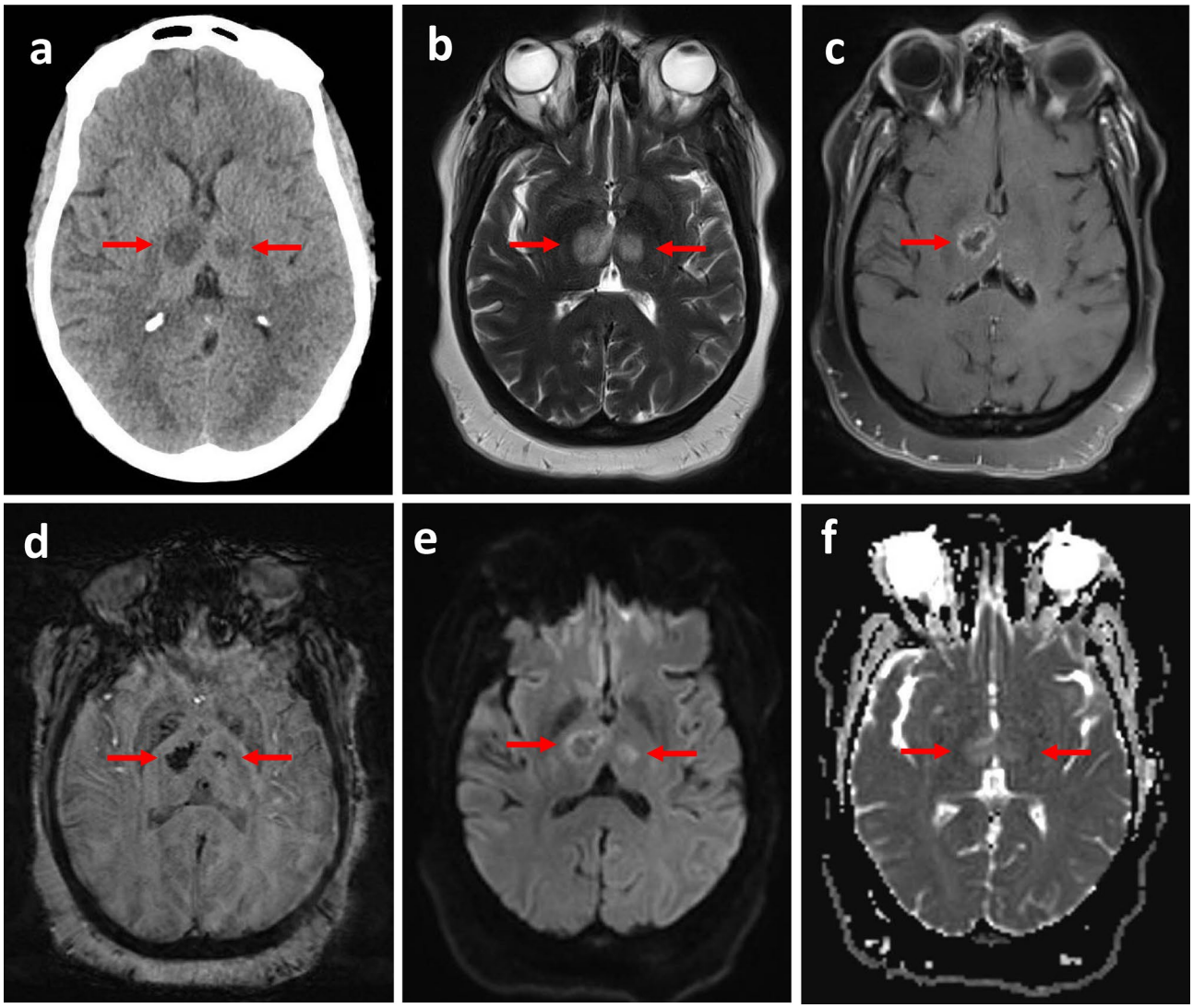

Fig. 1 Initial non-contrast head CT (**A**) showing hypodensities in the bilateral thalami. Brain MRI on admission demonstrating bilateral thalamic T2 FLAIR hyperintensies (**B**) with rim enhancement on postcontrast T1-weighted imaging (**C**). Foci of blooming artifact on susceptibility weighted imaging were seen in the bilateral thalami (**D**). No diffusion restriction was seen on diffusion-weighted and apparent diffusion coefficient imaging (**E**, **F**)

Metagenomic next-generation sequencing (mNGS), performed on CSF to evaluate broadly for infectious pathogens, did not detect presence of pathogenic nucleic acids. Ultimately, a brain biopsy targeting the right thalamus was obtained. Pathology showed perivascular neutrophilic inflammation suggestive of small vessel vasculitis with significant necrosis and hemorrhage in the surrounding brain parenchyma (Fig. 2). There was no evidence of demyelination or neoplasm.

After exclusion of alternative etiologies, the patient was diagnosed with COVID-19-associated ANE. She was treated with a 5-day course of high-dose methylprednisolone (1 g/day) which resulted in dramatic improvement of her aphasia and encephalopathy. Repeat lumbar puncture on hospital day 10 revealed normalization of protein (36 mg/dL) and cell count (3/mm3).

Repeat MRI following administration of steroids showed minimally decreased prominence of the left thalamic lesion but was otherwise stable. Following improvement of her aphasia, the patient endorsed recent exposure to COVID-19-positive contacts and subsequent cough, headache, and fatigue with symptomatic resolution 1–2 days before admission. The patient was discharged home on hospital day 14 with minimal residual speech deficits.

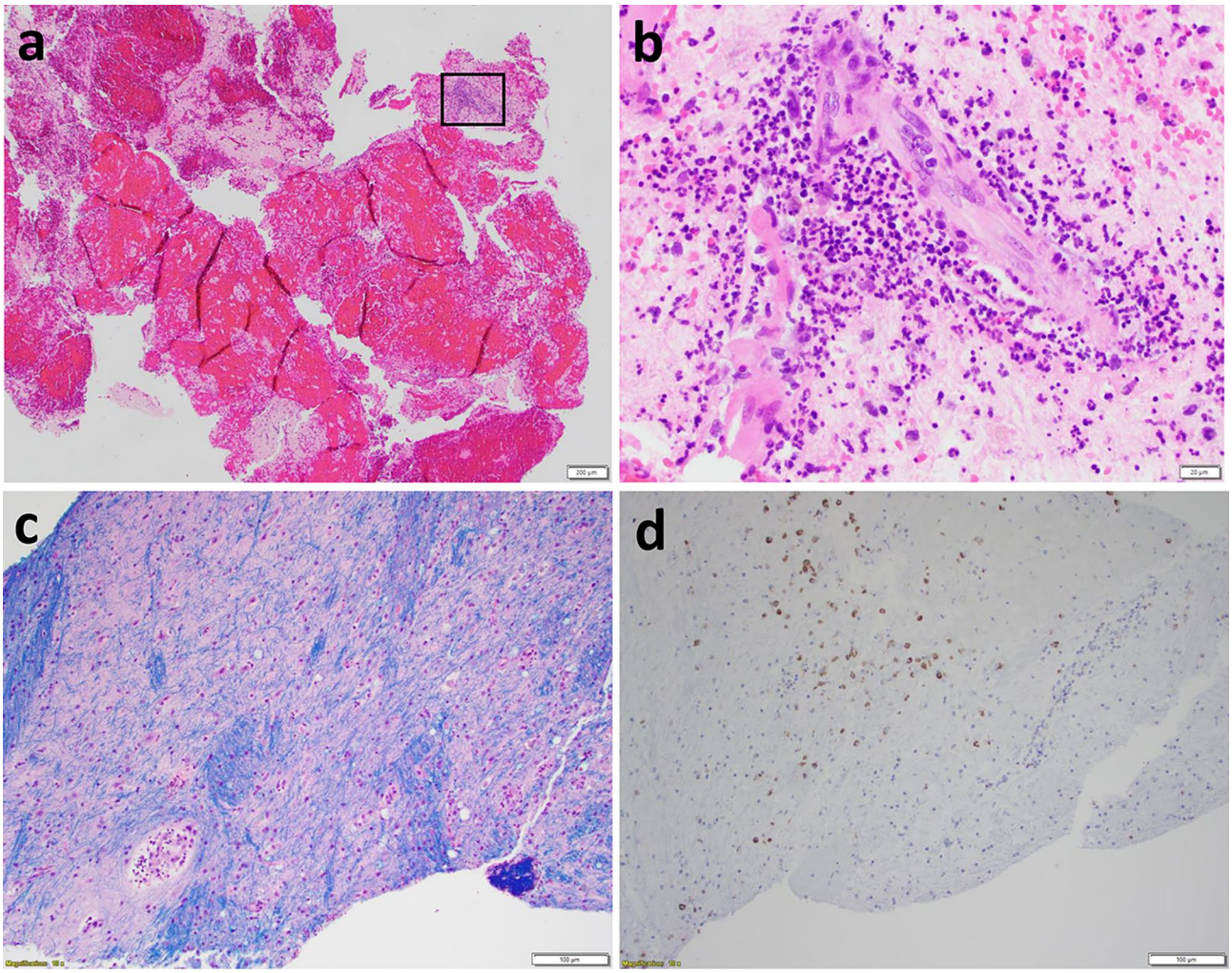

Fig. 2 Hematoxylin and eosin-stained sections of right thalamic biopsy. **A** Low power; extensive hemorrhage, necrosis, and perivascular inflammation. **B** High power; a reactive vessel with a dense, neutrophilic-predominant perivascular inflammatory infiltrate involving portions of the vessel wall. **C** Luxol fast blue stain showing myelinated fibers mostly in bundles, with an appropriate degree of myelination for the thalamus. **D** CD68 highlighting scattered macrophages, fewer than expected in an active demyelinating lesion, and without clear perivascular distribution

Discussion

We present a rare case of COVID-19-associated ANE diagnosed by clinical features and neuroimaging. Classically described in children following viral respiratory infections, ANE has been identified as a rare complication of SARS-CoV-2 infection (Mizuguchi 1997; Poyiadji et al. 2020; Elkady and Rabinstein 2020). Active respiratory symptoms are typically present during initial neurological presentation. Notably, symptoms in this case resolved before onset of neurological symptoms and accurate history were obscured by the patient's expressive aphasia. SARS-CoV-2 serologies may provide supportive evidence of preceding infection when accurate clinical history cannot be obtained. Progressive encephalopathy and seizures are common presenting features (Wu et al. 2015). The spectrum of severity is broad, ranging from mild cases with complete recovery to fatal presentations marked by rapid clinical decline (Wu et al. 2015). This case falls within the described clinical spectrum of ANE, representing a relatively benign course with involvement restricted to the bilateral thalami and remarkable recovery with corticosteroids. Characteristic MRI features include symmetric T2/FLAIR hyperintensities, often with rim-enhancement and associated blooming artifact (Wu et al. 2015). Thalamic involvement is present in all cases, with bilateral involvement considered highly characteristic of ANE (Wu et al. 2015). Absence of CSF pleocytosis is required in previously proposed diagnostic criteria for ANE; however, mild lymphocytic-predominant pleocytosis has been described in COVID-19-associated ANE (Mizuguchi

1997; Elkady and Rabinstein 2020). This case is the first to describe neutrophilic predominance.

The underlying pathogenesis of ANE is generally attributed to immune-mediated mechanisms, rather than direct viral cytopathic effects (Wu et al. 2015). A robust systemic immune response triggered by the antecedent infection produces a storm of inflammatory cytokines, resulting in blood brain barrier disruption (Wu et al. 2015). Subsequent edema, petechial hemorrhage, and necrosis occur. Right thalamic biopsy demonstrated perivascular neutrophilic inflammation with abundant necrosis and hemorrhage, consistent with previously described histopathology of ANE (Ng et al. 2010). No evidence of demyelination was seen, which if present, is more consistent with acute demyelinating encephalomyelitis or acute hemorrhagic leukoencephalitis. Given most cases of ANE are diagnosed based on clinical history of preceding infection and characteristic neuroimaging, this case provides a rare opportunity for direct radiological-pathological correlation, with only a single prior report in the literature attributable to SARS-CoV-2 and relatively few reports attributable to other viruses (Nersesjan et al. 2021; Ishii et al. 2015).

To our knowledge, this case is the first report of mNGS use in the evaluation of COVID-19-associated ANE, or ANE more broadly. Testing of the CSF for SARS-CoV-2 by reverse transcription-PCR (RT-PCR) has returned positive in only one prior case after repeated sampling (Virhammar et al. 2020). Absence of pathogenic nucleic acids by mNGS, generally more sensitive than RT-PCR for pathogen detection, is supportive of an underlying immune-mediated mechanism rather than direct viral effect (Wilson et al. 2019). However, SARS-COV-2 has been detected by RT-PCR, immunohistochemistry, and electron microscopy performed on brain tissue collected from patients with predominately respiratory manifestations of COVID-19 (Lou et al. 2021). Although robust systemic inflammation has been identified as a common antecedent event, whether the pathophysiology of ANE is predominately driven by direct viral invasion or an autoimmune response deserves further inquiry. Future study of autopsy specimens from patients with COVID-19-associated ANE would enable broader tissue sampling and may offer additional insights into the underlying pathogenesis.

Conclusion

The diagnosis of ANE is a clinicoradiologic diagnosis, and early recognition of characteristic neuroimaging is important given the potential for rapid clinical deterioration (Wu et al. 2015). In our case, the presence of atypical features, such as neutrophilic-predominant pleocytosis and the absence of active respiratory symptoms, prompted extensive diagnostic evaluation. In patients without active symptoms or clear history of preceding COVID-19 infection, positive SARS-CoV2 serologies should prompt early consideration of ANE.

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Author contribution All authors contributed to the study conception and design. Case report data collection and interpretation was performed by Leigh A. Rettenmaier, Lama Abdel-Wahed, Hisham Abdelmotilib, and Kyle S. Conway. The first draft of the manuscript was written by Leigh A. Rettenmaier and all authors revised the previous versions of the manuscript for intellectual content. All authors read and approved the final manuscript.

Declarations

Conflict of interest The authors declare no competing interests.

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