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A case report of lethal cerebral encephalocele and antiphospholipid antibiotic response following SARS-CoV-2 vaccination

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SUMMARY

Acute hemorrhagic encephalomyelitis (AHEM) is a relatively uncommon hyperacute form of acute disseminated encephalomyelitis (ADEM). The disease is distinguished by fulminant inflammation and demyelination of the brain and spinal cord, and it is frequently preceded by an infection or vaccination. A 53-year-old man with rheumatoid arthritis and ongoing methotrexate and etanercept treatment developed fatal AHEM after receiving the second dose of the COVID-19 vaccine. Multiorgan thromboembolic disease complicated the disease course, as did the presence of high/moderate levels of cardiolipin IgG antibodies and anti-beta-2 glycoprotein 1 IgG antibodies, indicating a possible antiphospholipid syndrome. Immunosuppressive therapy failed to improve the situation. Comprehensive clinical, neuroimaging, and neuropathological findings are included in the report. The case focuses on diagnostic challenges in a patient who has multiple diagnoses. preceding risk factors, such as autoimmune disease, immunotherapy, and vaccination, may have pathophysiological implications. Although evidence cannot be established, the temporal association with the COVID-19 vaccination may suggest possible causality. Reporting potential adverse events following COVID-19 vaccination is critical for identifying at-risk populations and achieving pandemic control.

Keywords: Cerebral encephalocele; Antibiotic; SARS-CoV-2.

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INTRODUCTION

Acute hemorrhagic encephalomyelitis (AHEM), also known as acute hemorrhagic leukoencephalomyelitis (AHLE/AHL) or Weston-Hurts Syndrome, is a rare, frequently fatal hemorrhagic variant of acute disseminated encephalomyelitis (ADEM). The pathogenic mechanisms are considered to involve immune-mediated blood vessel injuries, inflammation, perivascular demyelination, haemorrhage, and necrosis. Rapid neurological deterioration and mortality rates of up to 70% are common in AHEM, in contrast to the better prognosis of ADEM. AHEM, as well as ADEM, is frequently associated with an existing or previous infection or vaccination although post-vaccination ADEM is rare and represents only 5-10% of ADEM cases [1].

Several reports of ADEM after COVID-19 vaccination have recently been described, whereas the presence of AHEM phenotypes is only rarely reported. Furthermore, a wide range of neurological symptoms have been reported. In people infected with COVID-19, hemorrhagic vascular injuries, inflammation, and demyelination with features similar to ADEM and AHEM have been described. COVID-19 has been classified as a prothrombotic disease with hypercoagulability and endothelial cell injury, both of which are associated with inflammation. Thromboembolic events are common in COVID-19 patients, and antiphospholipid antibodies (aPL) are prevalent in critically ill patients.

A recent COVID-19 cohort study found that the presence of anti-phosphatidylserine/prothrombin (aPS/PT) IgG was associated with neurological symptoms. Antiphospholipid syndrome (APS) is an autoimmune multiorgan disease characterised by recurrent thromboembolic events, thrombocytopenia, and foetal loss, as well as cardiac, dermatological, and neurological manifestations and persistent antiphospholipid antibodies. A population-based study estimated the incidence of APS in the general adult population to be 2.1/100,000 and the prevalence to be 50/100,000. Patients with aPL antibodies are more likely to have them. with autoimmune diseases, infections, cancer, and systemic inflammatory diseases [2,3].

A wide range of CNS manifestations including cerebrovascular disease and demyelinating disease have been linked to both APS and the presence of aPL antibodies, and APS is an important differential diagnosis to consider for patients with symptoms and signs of CNS inflammatory

disease. Following the second Pfizer-BioNTech COVID-19 vaccination, a patient developed AHEM, systemic venous thromboembolism, and the presence of moderate/high levels of aPL antibodies, indicating a possible APS. The case illustrates the diagnostic and therapeutic challenges in a patient with fulminant CNS inflammation and thromboembolism, as well as complicating preceding autoimmune disease, immunosuppressive treatment, and vaccination.

LITERATURE REVIEW

Over a few hours, a 53-year-old man developed confusion and unconsciousness and presented to the emergency room with a Glascow Coma Scale of 7, agitation, and snoring. He had received his second Pfizer-BioNTech COVID-19 vaccine injection two days before. An anisocoria, right side miosis, bilateral absence of pupillary light reflex, and reduced voluntary movements in the left arm and leg were discovered during a neurological examination. The patient was afebrile without clinical or laboratory signs of infection. He was placed in the intensive care unit after being intubated (ICU). Previous medical history included rheumatoid arthritis (RA) with ongoing etanercept and methotrexate treatment. Acute brain computed tomography (CT) revealed a small hypoattenuating area in the left temporal lobe, which was interpreted as an acute/subacute ischemic lesion, as well as reduced perfusion in the brain.

The left hemisphere, and normal CT angiography. MRI revealed multiple cortical and subcortical lesions with high T2 and FLAIR signals, as well as widespread petechial haemorrhages. Repeated MRI scans revealed significant neuroradiological progress, including the development of widespread lesions in the cortical grey matter, thalami, basal ganglia, corpus callosum, brainstem, and cerebellum. Multiple lesions were found in the cervical and thoracic medulla, mostly in grey matter. Cortical laminar necrosis, a decrease in brain swelling, and regional encephalomalacia appeared three weeks later, in addition to increasing bilateral confluent lesions with increased signal in FLAIR and DWI, possibly representing delayed demyelination [4].

The initial suspected diagnosis was ischemic stroke, and the patient received intravenous thrombolysis 3.5 hours after the onset of symptoms. With the suspicion of encephalitis or ADEM, the diagnosis was re-evaluated after diagnostic work-up and treatment with acyclovir and high dose intravenous steroids (betamethasone 32 mg/day, day 2-4, followed by methylprednisolone 1 g/day for 5 days, two cycles, day 5-16). The term "responsibility" refers to the act of determining whether or not a person is responsible for his or her own actions. From day seventeen, oral steroids (prednisolone 50 mg/day with slow tapering) were administered. Despite treatment with full dose dalteparin, the patient developed bilateral pulmonary embolism (day two) and venous brachial thrombosis (day four). Heparin at full strength.

DISCUSSION

Diagnostic criteria for AHEM have not been defined but the present case fulfils the criteria of ADEM. Aside from ADEM/AHEM, the proposed differential diagnoses included ischemic stroke or vasculitis with hemorrhagic transformation, infectious meningoencephalitis, autoimmune encephalitis, and COVID-19-related disease. The initial MRI findings were similar to those seen in HSV encephalitis, but similar pathologies have also been found in AHEM cases. The neuroimaging development and the negative microbiological screening ruled out HSV. Due to the focal cortical lesions with diffusion restriction, other early differential diagnoses included embolic infarctions or primary CNS vasculitis. However, the flocculus lesions and spinal cord lesions were thought to be unlikely locations for ischemic infarctions, so this diagnosis was ruled out. Furthermore, the normal CT angiography and the subsequent progressive enlargement of brain lesions were performed. not compatible with vasculitis.

COVID-19 associated encephalitis was also considered a possible diagnosis because it has been linked to similar neuroimaging and neuropathological findings to AHEM. However, the clinical course, PCR tests, and thoracic CT examination revealed no evidence of COVID-19. Interestingly, the present case had several similarities with three COVID-19 vaccine-associated AHEM cases recently described in a report from Germany. These patients were characterised by rapid severe clinical deterioration and coma, neuroimaging findings of bilateral white and grey matter supratentorial lesions with hemorrhagic involvement, absence of CSF-OCB, and poor outcome. In contrast to our case, these three patients developed symptoms after their first COVID-19 injection, whereas the present case developed symptoms after his second injection. ADEM has primarily been described as a "first vaccine event," which is consistent with the three German cases.

It is possible that methotrexate and etanercept treatment only elicited a weak immune response to the first COVID-19 vaccine injection in our patient, while the second did not. The injection resulted in a stronger vaccine response. Patients with chronic inflammatory disease and treatment with tumour necrosis factor-a inhibitors had lower antibody responses after COVID-19 vaccination. The absence of aPL antibodies was reported in 1/3 of the German AHEM cases while no information about aPL antibody testing or results in the two other patients was given. Previous case reports on COVID-19 vaccine-associated ADEM have occasionally described negative aPL antibodies, but information on testing and results is generally scarce. To the best of our knowledge, AHEM and possible APS following COVID-19 vaccination has previously not been reported in the literature.

The mechanisms underlying vaccine-induced ADEM are unknown, but autoimmune reactions involving molecular mimicry between vaccine components and endogenous CNS structures have been proposed to play a role. Through anti-ganglioside antibodies, molecular mimicry appears to be involved in COVID-19 induced Guillain-Barré syndrome, supporting similar pathophysiological

mechanisms in CNS demyelinating diseases. There are also considerations regarding mRNA vaccines that may trigger a type 1 IFN response and aPL antibody production leading to the thrombotic manifestations associated even to CAPS. A few cases of CAPS onset soon after the first dose of mRNA COVID-19 vaccine have been described, and it has been speculated that the vaccination may have acted as a "second-hit" triggering CAPS in people with an aPL positive serological background [5].

CONCLUSION

Longitudinal observational studies are needed to assess a possible causal link between COVID-19 vaccination and ADEM/AHEM and to improve knowledge about risk groups for vaccination and infection, especially when the latter is eventually milder.

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CONFLICT OF INTEREST

The authors certify no conflict of interest with any financial organization about the material described in the manuscript.

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