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INFLUENZA A-ASSOCIATED ACUTE NECROTIZING ENCEPHALOPATHY IN AN IMMUNOCOMPETENT ADULT

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ABSTRACT

Introduction: Acute necrotizing encephalopathy (ANE) is a rare but severe neurological condition, typically triggered by viral infections, including influenza. It is characterized by a dysregulated immune-inflammatory host response, leading to rapid neurological deterioration, including encephalopathy and multifocal brain lesions. Diagnosis and treatment are challenging, and the condition is associated with high morbidity and mortality.

Case description: We report the case of a 48-year-old immunocompetent male who presented twice to the emergency department with fever and rapidly progressing altered consciousness, followed by generalized seizures. Neuroimaging revealed characteristic bilateral thalamic lesions and diffuse cerebral haemorrhage. Rapid diagnostic testing confirmed influenza A virus infection, leading to the diagnosis of influenza-associated acute necrotizing encephalopathy. Despite the initiation of antiviral therapy with oseltamivir, along with high-dose intravenous corticosteroids and immunoglobulins, the patient passed away due to severe neurological complications.

Discussion: Adult-onset ANE is exceptionally rare, particularly in Western populations, and is associated with a fulminant clinical course. Common features include altered mental status and seizures, often progressing to severe outcomes despite treatment. Given its non-specific prodromal symptoms and rapid neurological decline, early recognition and prompt neuroimaging are essential for diagnosis and management. Increased awareness of this condition among clinicians may facilitate earlier intervention and potentially improve outcomes.

Conclusion: The present case report highlights the fatal outcome of ANE as a rare complication of Influenza A infection in an immunocompetent adult.

KEYWORDS

Necrotizing encephalopathy, encephalitis, influenza A, H1N1

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LEARNING POINTS

- Acute necrotizing encephalopathy (ANE) in the setting of Influenza A infection clinically manifests with high-grade fever and neurological semiology, including diplopia and epileptic episodes as seen in this patient.
- Core therapeutic management of ANE involves the administration of oseltamivir, intravenous corticosteroids and gamma globulin.
- The present case report underlines the abrupt clinical deterioration of an immunocompetent patient with Influenza A-induced ANE, over a 3-day onset of flu-like symptoms.

INTRODUCTION

Acute necrotizing encephalopathy (ANE) is a rare, but severe neuroinflammatory condition, typically characterized radiologically by bilateral, symmetrical lesions of the thalami, and can potentially progress to haemorrhagic necrosis of the brain parenchyma[1]. It is predominantly associated with viral infections and can lead to systemic inflammatory responses, acute encephalopathy, and significant neurological impairment. Among the viral aetiologies, Influenza A has been well-documented as a causative agent, with initial descriptions of ANE linked to Influenza A infections emerging from paediatric cases in Japan in 1995[2].

The pathogenesis of ANE remains incompletely understood; however, the most widely accepted hypothesis involves a hyperinflammatory cytokine response, particularly mediated through the interleukin-6 (IL-6) signalling pathway. This cytokine storm is believed to disrupt the integrity of the blood-brain barrier, leading to cerebral oedema, vascular injury, and ultimately necrosis of neuronal tissue. An alternative mechanism suggests that the virus may gain access to the central nervous system via transaxonal spread along olfactory neurons[3].

To date, there is no established standard of care for influenza-associated ANE. Given the likely immune-mediated pathophysiology, therapeutic strategies have included antiviral agents such as high-dose oseltamivir and various immunomodulatory treatments, including corticosteroids, intravenous immunoglobulin, and cytokine inhibitors[4].

ANE has primarily been reported in the paediatric population, particularly in East Asian countries, and adult cases remain rare, especially among Caucasian individuals in Western countries[5]. The isolated examples of ANE in adults highlight the need for increased clinical awareness and thorough documentation of atypical cases. In this report, we present a case of influenza-associated ANE in a 48-year-old man in Greece, aiming to contribute to the growing literature and to raise awareness regarding the serious complications triggered by influenza in adults in European countries.

CASE DESCRIPTION

A 48-year-old previously healthy man initially presented to the emergency department with a 3-day history of fatigue, malaise and fever, with a recorded maximum temperature of 38°C. Initial evaluation, including complete blood count, serum biochemistry, and chest radiography, revealed no significant abnormalities. Rapid antigen testing for severe acute respiratory syndrome coronavirus 2 and influenza A and B viruses was negative. The patient was discharged with a diagnosis of a viral illness and was advised to follow conservative treatment measures at home.

Approximately 6 hours later, he returned to the emergency department via ambulance due to a new onset of generalized weakness and severe dizziness. Upon arrival, the patient was alert, interactive and fully oriented to person, place, and time, with a Glasgow Coma Scale (GCS) of 15/15. No focal neurological deficits were observed at this stage. Vital signs were stable: blood pressure 108/69 mmHg, heart rate 89 beats per minute, respiratory rate within normal limits, oxygen saturation 97% while breathing ambient air, and the patient was afebrile. An electrocardiogram demonstrated sinus tachycardia with no other abnormalities.

During further evaluation, the patient developed acute-onset diplopia. Neurological consultation was obtained, and during further observation, the patient progressively became disoriented, exhibiting confusion regarding time and place. Cranial nerve examination remained intact. An emergent non-contrast computed tomography scan of the brain was performed, revealing diffuse hypodensity in the brainstem and the upper cerebellar structures, as well as the basal ganglia *(Fig. 1)*. A lumbar puncture was performed under neurological supervision, and cerebrospinal fluid (CSF) was sent for laboratory analysis, including cytology, cultures, and viral polymerase chain reaction (PCR) *(Table 1)*. Shortly afterward, the patient developed generalized tonic-clonic seizures, followed by episodes of emesis. Seizure activity was controlled with intravenous administration of levetiracetam (1 g) and diazepam (10 mg). Given concerns about potential airway compromise and progressive neurological deterioration, the patient was electively intubated and transferred to the intensive care unit (ICU) for further monitoring and management.

Twenty-four hours after ICU admission, magnetic resonance imaging (MRI) with angiography of the brain was conducted. The imaging revealed multifocal ischemic changes affecting both anterior and posterior circulations, including the basilar artery and cervical spine. Diffuse hemorrhagic lesions were observed throughout the cerebral parenchyma, significantly impacting the brainstem, pons, and midbrain, with radiological evidence suggesting central brain herniation. No embolic source was detected *(Fig. 1)*.

Given the clinical and radiological findings, viral encephalitis was included in the differential diagnosis. Empirical intravenous therapy with ceftriaxone, vancomycin, and acyclovir was initiated, pending the results of the PCR.

A nasopharyngeal swab tested positive for Influenza A (H1N1) virus using everse transcription quantitative real-time PCR (RT-qPCR). Additional laboratory investigations revealed markedly elevated inflammatory markers, including an interleukin-6 (IL-6) level of 96 pg/ml (normal <6.4 pg/ml) and D-dimer of 10.02 mg/l (normal <0.5 mg/l). Notably, procalcitonin and C-reactive protein levels remained low at 0.09 ng/ml (normal <0.1 ng/ml) and 0.6 mg/dl (normal <0.5 mg/dl), respectively. An autoimmune panel, including antinuclear antibodies, anti-neutrophil cytoplasmic antibodies, rheumatoid factor, and anti-double-stranded deoxyribonucleic acid was negative.

Additional CSF analysis by multiplex PCR returned negative results for a broad panel of viral, bacterial, and fungal

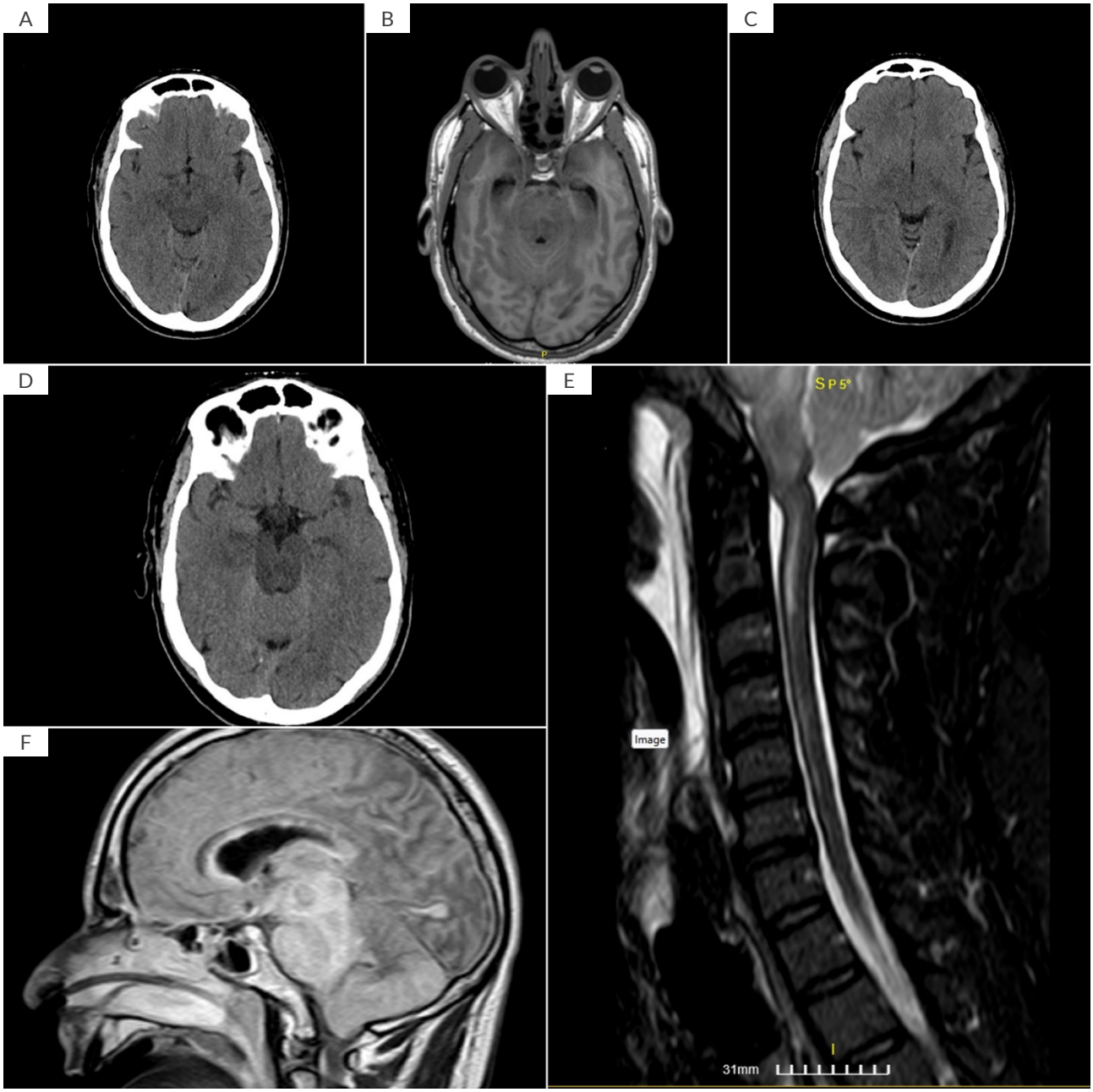


Figure 1. Brain computed tomography imaging demonstrating: A) Hypodensities in the corpus callosum, the right temporo-occipital region, and both thalami. The basilar artery appears patent and slender, with no evidence of thrombosis; B) Extensive abnormal signal with diffusion restriction, suggesting cytotoxic edema. Foci of signal loss on the gradient echo sequence indicate hemorrhagic infiltration. The vertebral and basilar arteries are slender but patent, likely due to exerted pressure; C) Attenuation of normal parenchymal distinction in the basal ganglia and parietal-occipital cortical parenchyma; D) Hypodense appearance of the brainstem and bilateral basal ganglia. Magnetic resonance imaging demonstrates; E) Hyperintense signal in the cervical spinal cord, depicting extension of the inflammation into the entire nervous system, indicative of spinal cord involvement in the context of severe extensive acute necrotizing encephalopathy; F) Fluid-attenuated inversion recovery sequences with hyperintense signal encompassing the entire brainstem, cerebellum, basal ganglia and corpus callosum, along with reduced definition of the cortical surface of the cerebral parenchyma.

Laboratory Test	Results	Reference range
Serum		
White blood cells (×10³/µl)	3.5	3.8-10.5
Polymorphonuclear neutrophils (%)	47.9	40-75
C-reactive protein (mg/dl)	2.1	<0.5
Aspartate transaminase (U/l)	56	<34
Alanine transaminase (U/l)	96	10-49
Serum glucose (g/dl)	72	6
CSF analysis		
White blood cells (×mm³)	2	<5
Red blood cells (×mm³)	5	<5
Total protein (mg/dl)	111.1	15-45
Glucose (mg/dl)	64	40-75 (60% of serum level)

Abbreviations: CSF, cerebrospinal fluid.

Table 1. Serum and CSF laboratory profile.

pathogens, including cytomegalovirus, varicella zoster virus, herpes simplex virus types 1 and 2, Epstein–Barr virus, human herpesvirus 6, enterovirus, parechovirus, West Nile virus, *Haemophilus influenzae*, *Listeria monocytogenes*, *Neisseria meningitidis*, *Escherichia coli* K1, *Streptococcus agalactiae*, *Streptococcus pneumoniae*, and *Cryptococcus neoformans/gattii*.

Based on the characteristic MRI findings, rapid neurological deterioration, positive Influenza A (H1N1) result, and the exclusion of other infectious, autoimmune, and neoplastic etiologies, a diagnosis of ANE secondary to Influenza A infection was made.

Treatment included high-dose oseltamivir (150 mg twice daily for 13 days), pulse corticosteroid therapy (methylprednisolone for 5 days), intravenous immunoglobulin (IVIG for 5 days), and enoxaparin (6,000 IU). On ICU day 3, the patient developed diabetes insipidus, likely due to involvement of the hypothalamic-pituitary axis, and was treated with mannitol.

Despite aggressive supportive care and immunomodulatory therapy, the patient's condition continued to deteriorate, and he passed away on ICU day 20.

DISCUSSION

ANE is a neurological complication of influenza infection with life-threatening sequelae. Prior to encephalopathy, patients typically experience symptoms of upper respiratory tract viral infection (i.e., fever, nasal discharge, myalgias/arthralgias, etc.). This case report highlights the rapid onset of mental deterioration/ANE and lethargy within 3 days of flu-like clinical manifestations.

It has been reported that central nervous system penetration may be mediated by the infection of the olfactory nerve. Proinflammatory cytokines produced in response to viral infection affect the vascular endothelium, leading to increased blood-brain barrier permeability, which causes cell death in neurons and glia[3].

The diagnostic approach to influenza-related ANE presents considerable challenges and is still considered a diagnosis of exclusion. CSF analysis typically shows increased total protein levels without pleocytosis, and radiological findings reveal hypodensities suggestive of bilateral necrosis of the thalami, with involvement of the brainstem and cerebellum. Moreover, influenza identification is reported to be facilitated through respiratory tests rather than CSF analysis[6].

Antiviral therapy with oseltamivir, intravenous corticosteroids, and gamma globulin is a fundamental therapeutic strategy for ANE, along with the administration of hyperosmolar agents and plasma exchange, where indicated[7]. In a similar case report involving a 46-year-old woman with an unremarkable medical history, influenza-B-related ANE was successfully treated with a double dose of oseltamivir, methylprednisolone pulses, and IVIG[8].

Our patient was not vaccinated against influenza; however, solid data on the prevention of neurologic complications among immunized individuals are absent. In general, the effectiveness of vaccination in eliminating influenza infections among adults, as estimated by relevant studies for the period 2024-2025, is 36-54% in outpatient settings[9], with a secondary infection risk among unvaccinated household contacts of 18.8%[10].

CONCLUSION

This case report illustrates the fatal consequences of influenza A-associated ANE in a healthy, immunocompetent adult. The lack of definitive diagnostic criteria due to the unclear etiopathogenesis of the disease hampers the diagnostic process. Further elucidation of the pathophysiological mechanisms of disease onset and progression, as well as vaccination strategies, will enable prompt diagnosis and effective infection control.

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