Case Report

A rare presentation of autoimmune limbic encephalitis with anti-Yo antibodies: Case report

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Abstract

Introduction: Paraneoplastic limbic encephalitis is a non-metastatic complication of malignant disease characterized by subacute neuropsychiatric symptoms and short-term memory deficits.

Case: We present an atypical case of a 38-year-old, previously healthy female with recurrent seizures, severe persistent short-term memory loss, and emotional lability. The patient was diagnosed with autoimmune limbic encephalitis confirmed by magnetic resonance imaging findings and positive anti-Yo antibodies. She screened negative for occult malignancies. The patient responded to daily prednisone and intravenous immunoglobulins and her cognitive deficits were resolved.

Conclusion: This is an unusual case of autoimmune encephalitis as anti-Yo antibodies are typically associated with cerebellar dysfunction. Our patient's case adds to the one other published case showing induction of limbic encephalitis due to anti-Yo antibodies, and prompts consideration of paraneoplastic anti-Yo limbic encephalitis as a rare cause of symptoms in patients with limbic encephalitis-like symptoms and no known etiology.

Keywords: Paraneoplastic syndrome, Encephalitis, Anti-Yo antibodies

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Introduction

Autoimmune encephalitis is a rare disease characterized by immune-mediated destruction of neurons in the central nervous system (CNS). Limbic encephalitis is one of the most common phenotypes of autoimmune encephalitis. Patients with limbic encephalitis typically present with subacute neuropsychiatric symptoms including mood and sleep disturbances, seizures, hallucinations, and short-term memory deficits that can progress into dementia (1,2).

Paraneoplastic encephalitis is a subtype of autoimmune encephalitis secondary to an immune response as a non-metastatic complication of malignant disease. Paraneoplastic limbic encephalitis occurs in around 1 in 10,000 patients with cancer (3). In many patients, paraneoplastic encephalitis can precede the diagnosis of cancer. Therefore, it is important to screen for malignancy in all patients with autoimmune encephalitis to identify occult tumours. Treatment of underlying malignant disease may also improve the neuropsychiatric symptoms of autoimmune encephalitis (2).

In younger patients with autoimmune encephalitis, misdiagnosis is unfortunately common, with symptoms often attributed to psychosis, drug abuse, or malingering (1). Here, we present the case of a previously healthy young adult with new-onset seizures. She was diagnosed with autoimmune limbic encephalitis confirmed by magnetic resonance imaging (MRI) findings. Her case was atypical as she tested positive for anti-Yo antibodies, typically associated with cerebellar degeneration rather than limbic encephalitis (2).

Autoimmune encephalitis is an uncommon cause of neuropsychiatric symptoms. This case highlights a rarely seen variant with an atypical presentation of anti-Yo antibody syndrome presenting with a primary limbic encephalitis presentation.

Case presentation

A 38-year-old female presented to the hospital with acute generalized-onset seizure, confusion, and disorientation. The generalized-onset seizure episode was witnessed and described as lasting five minutes with tonic-clonic (stiffening with twitching or jerking) movements, facial flushing, diaphoresis (sweating), and dilated pupils with no incontinence or tongue biting. In the month leading up to this episode, the patient described episodes of flushing and sweating without any loss of consciousness or seizures. Her past medical history was significant only for anxiety and recreational cannabis use. She had normal development and no history of previous seizures. Her home medications included citalopram and lorazepam.

On initial assessment, the patient had mild confusion, but otherwise her physical examination was unremarkable. She was afebrile. On initial neurological review she had appropriate affect, no obvious memory deficit, and normal pupillary function, visual fields, and eye movements. Power, tone, coordination, and gait were also normal. The patient had no symptoms of photophobia or headaches. The patient was discharged home with follow-up with outpatient neurology.

Three months later, the patient returned to hospital with psychosis, seizure, and decreased level of consciousness. Toxicology screen was only positive for tetrahydrocannabinol (THC), the psychoactive substance in marijuana. The patient was admitted to the intensive care unit and continued to have severe persistent short-term memory and cognitive deficits, as well as emotional lability, for the next two weeks with no improvement.

Diagnosis

The patient presented with a constellation of seizures, severe persistent short-term memory loss, and emotional lability. Pheochromocytoma (a catecholamine-secreting adrenal gland tumour) and carcinoid syndrome (paraneoplastic syndrome secondary to a carcinoid tumour, which often presents as flushing and diarrhea) were suspected on initial presentation due to the patient's episodes of flushed appearance and diaphoresis during the month leading up to the seizure as well as on presentation. However, the patient tested negative for 24-hour urine metanephrines and 5-hydroxyindolacetic acid. Pheochromocytoma and carcinoid syndrome also did not explain her subsequent short-term memory loss. Marijuana-induced toxicity was suspected based on the patient's elevated liver enzymes, and positive toxicology screen for THC. There are reports of cannabis-induced transient global amnesia which might have explained her short-term memory loss (4). However, the patient had severe persistent short-term memory loss for over two weeks with no signs of improvement, whereas marijuana-induced amnesia usually does not cause loss of memory for over 48 hours (5).

A CNS infection was considered due to elevated leukocytes (18×10^9/L); however, the patient was afebrile and had no other symptoms of infectious meningoencephalitis such as photophobia and headache. Cerebrospinal fluid (CSF) and serum were sent for Gram stains, cultures, and viral studies (including West Nile IgM, HIV p24 antigen, HIV 1/2 antibodies and HSV-1 and HSV-2), as well as Lyme disease IgM/IgG and VDRL antibody, which were all negative.

Other autoimmune encephalitides and CNS vasculitides were also considered but the patient tested negative for anti-NMDA-R antibody (autoimmune encephalitis), non-specific markers of encephalitis including anticardiolipin, ANA, anti-DNA antibody, and markers of ANCA-associated vasculitis (c-ANCA and p-ANCA). Both non-invasive vascular imaging and inflammatory markers did not suggest a pattern of vasculitis.

Finally, the MRI revealed hyperintensities in the medial temporal lobes (Figure 1). These findings, with new generalized-onset seizures and prolonged memory loss, prompted the consideration of limbic encephalitis. A lack of CSF pleocytosis and normal CSF protein level, along with a negative anti-NMDA-R antibody test, prompted a search for more unusual causes of limbic encephalitis. The patient's paraneoplastic panel returned positive for anti-Yo antibodies confirmed with western blot analysis, with 100% sensitivity and 100% specificity as per the manufacturer-validated test characteristics (6).

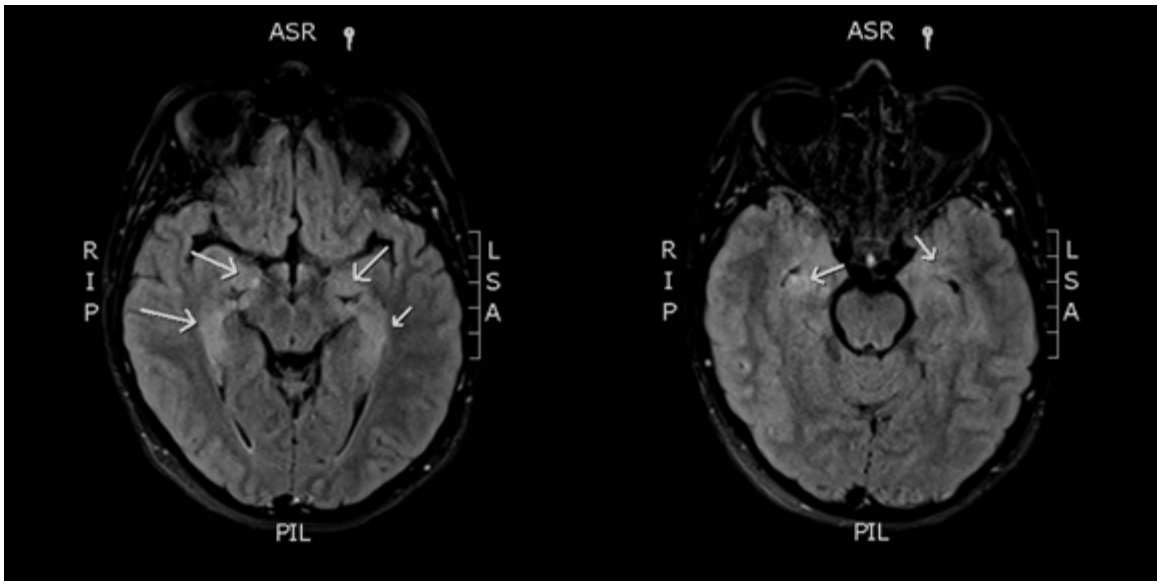

Figure 1. T2-weighted fluid-attenuated inversion recovery MRI showed hyperintensities (arrows) in the medial and posterior temporal lobes. This is a finding suggestive of limbic encephalitis.

Since the patient tested positive for the anti-Yo paraneoplastic antibody, she was investigated for occult malignancies. Screening computerized tomography (CT) scan of her chest, abdomen, and pelvis, and an ultrasound of her abdomen and pelvis, showed no findings of malignancy. A screening tumour marker panel was negative, including carbohydrate antigen 19-9, carcinoembryonic antigen, and cancer antigen 125. A subsequent screening mammogram showed asymmetric densities in both breasts. Follow-up ultrasound testing revealed complex cysts in the right breast and hypoechoic nodules thought to be fibroadenoma.

Management

Following a clinical diagnosis of limbic encephalitis, the patient was treated using the BrainWorks Antibody-Mediated Inflammatory Brain Disease protocol which includes daily prednisone and intravenous immunoglobulin (IVIG) to suppress the autoimmune response (7). The patient was also started on antiepileptic therapy including lamotrigine, clonazepam, and clobazam. Lamotrigine is an anticonvulsant that selectively inhibits sodium channels. Clonazepam and clobazam are anticonvulsants that are part of the benzodiazepine class. The patient's symptoms improved with treatment, and her cognitive deficits resolved.

Outcome and follow-up

The patient was discharged after 19 days in the hospital with outpatient neurology follow-up. Her Montreal Cognitive Assessment (MoCA) score was 29/30 two months post-discharge. A

repeat MRI six months after treatment revealed almost complete resolution of the abnormalities. A repeat electroencephalogram (EEG) showed normal features.

The patient's memory deficits and mood disturbances improved, but she continues to have rare focal seizures. Repeat paraneoplastic antibodies were negative, including anti-Yo antibodies. Repeat anti-NMDA-R antibodies have been negative in the serum and CSF.

Discussion

Paraneoplastic limbic encephalitis is a rare non-metastatic complication of malignancy characterized by immune-mediated destruction of neurons. Patients typically present with subacute neuropsychiatric symptoms including mood and sleep disturbances, seizures, hallucinations, and short-term memory deficits that can progress into dementia (1,2). The diagnosis of paraneoplastic limbic encephalitis is based on a combination of clinical symptoms and paraneoplastic antibodies, as well as MRI and EEG findings. Fluid-attenuated inversion recovery (FLAIR) MRI will show hyperintense regions in the medial temporal lobe in 70–80% of patients with limbic encephalitis (2). EEG can show epileptic or generalized slow activity in the temporal lobes. There are a variety of autoimmune antibodies associated with limbic encephalitis, including those against extracellular antigens such as NMDA-R and LGI1 and intracellular antigens such as anti-Hu and anti-Ma2. It is worth noting that approximately 40–50% of patients with clinical symptoms of limbic encephalitis will test negative for paraneoplastic antibodies (2). Limbic encephalitis is also rarely associated with anti-Yo antibodies (2). Our patient showed classic signs of limbic encephalitis including seizures, mood disturbances, and short-term memory deficits. This is correlated with MRI findings of hyperintense signals in the medial temporal lobes. She tested positive for anti-Yo antibodies, but not other antibodies commonly associated with limbic encephalitis such as anti-Hu and anti-NMDA-R. Furthermore, our patient demonstrated positive response to immunosuppression with IVIG and corticosteroids.

In approximately 70% of patients with paraneoplastic limbic encephalitis, neurological symptoms will be the first presentation of malignancy (2). Therefore, all patients diagnosed with paraneoplastic limbic encephalitis should be screened for occult tumours using chest and abdominal CT scans, and pelvic ultrasound repeated at increasing intervals to screen for occult tumours. Approximately 70–80% of patients with paraneoplastic neurological syndromes will screen positive for cancer upon imaging (2). Early detection and treatment of malignancy is important for patient recovery.

From our literature search for anti-Yo antibodies and limbic encephalitis, we were able to find only one other case describing a 61-year-old patient presenting with limbic encephalitis, colon adenocarcinoma, and anti-Yo antibodies (8). The patient was not responsive to treatment and remained ventilator-dependent in a permanent vegetative state with no improvement in neurological status (8). The similarities between the two cases is that both patients presented with neurological disturbances, seizures, hyperglycemia, and metabolic acidosis. They also had findings suggestive of limbic encephalitis on MRI and tested positive for anti-Yo antibodies. The

difference between the cases is that our patient is a younger individual, with no currently detectable occult cancers on imaging. Furthermore, our patient responded to corticosteroids and IVIG with improvement in short-term memory and cognition, while the other patient remained in a vegetative state. Nevertheless, these two cases indicate that anti-Yo antibodies may lead to limbic encephalitis in rare circumstances.

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