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Case report

Thymoma associated paraneoplastic encephalitis (TAPE), a potential cause of limbic encephalitis

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Accepted 21 August 2019

SUMMARY

A 59-year-old man presents with expressive aphasia and short term memory deficits. Shortly thereafter, he started developing staring spells and intermittent right hand spasms, preliminarily thought to be simple partial seizures. Subsequent MRI brain imaging was highly suggestive of herpes simplex virus (HSV) encephalitis; however, HSV PCR from cerebrospinal fluid was negative. On further testing, the patient was found to have an autoimmune encephalitis thought to be related to an incidentally found thymoma. His clinical presentation, in conjunction with imaging and response to therapy, was strongly suggestive of thymoma associated paraneoplastic encephalitis. Early recognition is the only way to ensure prompt initiation of appropriate treatment. Immunotherapy and cancer directed therapy (including tumour resection, if indicated) have been shown to have favourable outcomes, improved speed of neurological recovery and reduced risk of relapses. Without treatment, progressive neurologic deterioration can occur over months to years, eventually resulting in death.

BACKGROUND

Encephalitis is characterised by inflammation of the brain tissue; however, nearly half of all encephalitis-associated hospitalisations do not end up having a concrete, discernable diagnosis, despite thorough workup.¹ Encephalitis has a plethora of potential aetiologies, therefore a wide range of testing and differential diagnoses must be considered, including autoimmune and paraneoplastic encephalitis. What is now being more widely recognised in the literature than previously, autoimmune and paraneoplastic encephalitis have been reported to have significant morbidity and potentially fatal complications without prompt recognition and treatment. Approximately half of patients with a thymoma are also found to have paraneoplastic neurologic syndromes, the most common being myasthenia gravis.² However, these cases only involve the peripheral nervous system since autoimmune antibodies block or destroy muscular nicotinic acetylcholine receptors, and spare the central nervous system (CNS). There are limited case reports of thymoma associated paraneoplastic encephalitis (TAPE) involving inflammation of the limbic or extralimbic areas of the brain, which can potentially lead to progressive neurologic decline and death without proper diagnosis and treatment.³ Here we review an intriguing case report of a patient whose presentation was consistent with TAPE.

CASE PRESENTATION

A 59-year-old man with no significant medical history was in his usual state of health until 5 days prior to a visit to his primary care physician with a chief complaint of a 'strong bitter taste in his mouth'. This was associated with expressive aphasia, short-term memory deficits and confusion, all primarily noticed by his wife. Throughout his progressive development of symptoms, he also started having occasional staring spells, and intermittent right hand spasms, preliminarily thought to be simple partial seizures. He took no regularly scheduled medications, and had no known drug allergies. Medical and surgical history was only notable for benign colorectal adenomas. Social history included: never smoker, social alcohol user and no recreational or illicit drug use. He denied any recent travels outside of his local area and denied constitutional symptoms, fevers, chills, nausea, vomiting, lightheadedness, chest pain, or shortness of breath.

On presentation, his temperature was 99.0°F (37.2°C), blood pressure was 115/81 mm Hg, heart rate of 95 beats/min, respirations were 20 breaths/min, and oxygen saturation was 99% on room air. His body mass index (BMI) was 27.05 kg/m². Physical exam findings were significant for expressive aphasia, mild cognitive deficits most notably with short-term memory loss (unable to recall three simple items after 5 min). Remainder of neurological exam was unremarkable: cranial nerves 2-12 intact, no sensory or motor deficits, no limb ataxia and normal gait. Remainder of physical exam was unremarkable.

INVESTIGATIONS

His primary doctor ordered an outpatient MRI brain without contrast, which revealed a large confluent area of signal intensity involving the left medial temporal lobe and hippocampus. The patient was urgently referred to our hospital for further work up and evaluation.

On admission, his initial metabolic panel and complete blood count labs were unremarkable, with a white cell count of 9.9 x10⁹/L. A repeat MRI brain with and without contrast demonstrated T2/fluid-attenuated inversion recovery (FLAIR) hyperintensities of the left frontal and medial temporal lobe and right cingulate gyrus (which is part of the limbic system) with minimal enhancement (figure 1). Initial report from the neuroradiologist who reviewed the MRI images with the consulting inpatient neurologist determined that the findings



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To cite: Liu H, Edson RS. *BMJ Case Rep* 2019;**12**:e230709. doi:10.1136/bcr-2019-230709

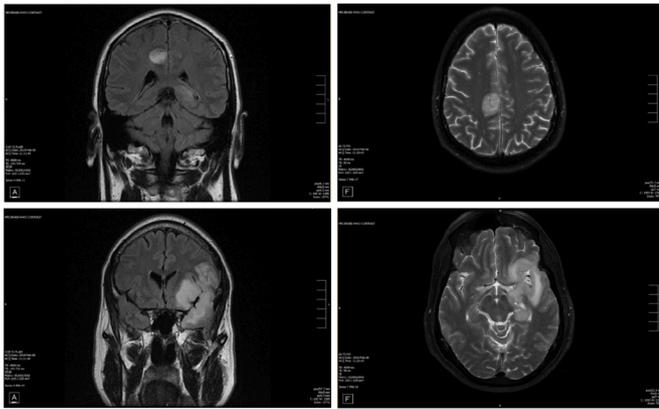


Figure 1 Axial and coronal views of MRI brain T2-weighted/fluid-attenuated inversion recovery sequences shown demonstrating predominantly R cingulate gyrus, L frontal and L medial temporal lobe hyperintensities.

were not suggestive of any sort of primary or metastatic malignancy, but, in fact, remarked that this pattern was pathognomonic for herpes simplex virus (HSV) encephalitis. A continuous electroencephalogram (EEG) showed abnormal left frontotemporal periodic lateralised epileptiform discharges (PLEDs) with probable electrographic seizures from the left temporal regions, also consistent with HSV encephalitis. However, lumbar puncture with cerebrospinal fluid (CSF) testing was negative for HSV 1&2 DNA amplification, and was also rather unsuggestive of infection (only showing elevated protein with no pleocytosis). However, given the MRI findings and clinical presentation, the patient was empirically treated with acyclovir (intravenous, 10 mg/kg/dose every 8 hours) for suspected HSV encephalitis, as the primary hospital team pursued further investigation.

During the course of the hospitalisation, his cognitive status continued to decline despite antiviral treatment, and his expressive aphasia also continued to worsen. Further serum and CSF analysis (sent to Mayo Clinic Laboratory) testing for an expanded autoimmune encephalitis panel only revealed a positive serum muscle acetylcholine receptor (AChR) binding antibody (table 1). It is important to note that muscle AChR antibody is associated with causing myasthenia gravis involving the peripheral nervous system. Ultimately, the full results of both the serum and CSF autoimmune encephalitis panel returned otherwise negative for the usual culprit biomarkers of autoimmune encephalitis, such as anti-N-methyl-D-aspartate (NMDA) receptor antibodies, voltage-gated potassium channel (VGKC) complex antibodies, leucine-rich glioma inactivated 1 (LGI1) antibodies, gamma-aminobutyric acid-B (GABA_B) receptor antibodies, glutamic acid decarboxylase 65 antibodies, contactin-associated protein 2 (CASPR2) antibodies and anti- α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antibodies. The muscle acetylcholine receptor antibodies were also positive in the serum, but, because they only target muscular receptors in the peripheral nervous system, they are not pathogenic to the CNS despite concurrent presence in the CSF (table 2). On further literature review, there have been a handful of case reports of very similar clinical presentations of suspected encephalitis in the setting of thymoma tumour found to have GABA_A or GABA_B receptor antibodies.⁴ Although the patient tested negative for GABA_B receptor antibodies, the status of anti-GABA_A receptor antibodies presence in this patient is unfortunately unknown due to lack of testing.

Table 1 CSF autoimmune encephalitis panel results

CSF autoimmune encephalitis panel (ENCEC)		
Result name	Result	Reference value
AChR (Muscle) Binding Ab	Positive	Negative
NMDA-R Ab CBA	Negative	Negative
VGKC-complex Ab IPA	0.00 nmol/L	0.00–0.02
LGI1-IgG CBA	Negative	Negative
CASPR2-IgG CBA	Negative	Negative
GAD65 Ab Assay	0.00 nmol/L	≤0.02
GABA _B -R Ab CBA	Negative	Negative
AMPA-R Ab	Negative	Negative
ANNA-1	Negative	<1:2
ANNA-2	Negative	<1:2
ANNA-3	Negative	<1:2
AGNA-1	Negative	<1:2
PCA-1	Negative	<1:2
PCA-2	Negative	<1:2
PCA-Tr	Negative	<1:2
Amphiphysin Ab	Negative	<1:2
CRMP-5-IgG	Negative	<1:2

AChR, acetylcholine receptor; AMPA, anti- α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; AGNA-1, anti-glial/neuronal antibody type 1; ANNA-1, antineuronal nuclear type 1 antibodies; ANNA-2, antineuronal nuclear type 2 antibodies; ANNA-3, antineuronal nuclear type 3 antibodies; CASPR2, contactin-associated protein 2; CBA, cell-based assay; CRMP-5-IgG, collapsin response-mediator protein-5-IgG; CSF, cerebrospinal fluid; ENCEC, encephalitis panel CSF; GABA_B, gamma-aminobutyric acid-B; GAD65, glutamic acid decarboxylase 65; LGI1, leucine-rich glioma inactivated 1; NMDA, anti-N-methyl-D-aspartate; PCA-1, Purkinje cell cytoplasmic type 1 antibodies; PCA-2, Purkinje cell cytoplasmic type 2 antibodies; PCA-Tr, Purkinje cell cytoplasmic type Tr antibodies; VGKC, voltage-gated potassium channel.

Furthermore, a CT chest/abdomen/pelvis with contrast, as well as a whole body PET-CT scan, was performed to rule out occult primary malignancy. From this workup the patient was found to have bilateral subsegmental pulmonary emboli, and a partially calcified 4.0×2.3×1.5 cm anterior mediastinal mass, most likely representative of a thymoma (figure 2).

DIFFERENTIAL DIAGNOSIS

This case involves an immunocompetent host who presented with a rather rapid and acute development of expressive aphasia, cognitive impairment (short-term memory deficits), staring spells, and intermittent right hand spasms. The differential diagnosis considered for this clinical presentation included infectious causes (viral/bacterial encephalitis), vascular causes (cerebrovascular accident), seizures and primary psychiatric disorders (acute psychosis or schizophrenia), among others.

Viral and bacterial meningitis causing encephalitis are perhaps the most common causes of acute encephalitis in an otherwise healthy individual, though, as mentioned earlier, the epidemiology landscape of this may be shifting as we develop more testing abilities for determining other aetiologies of encephalitis. There is a wide range of infectious aetiologies including herpes simplex virus, West Nile virus, *Neisseria meningitidis* and *Listeria monocytogenes*, just to name a few. However, given the lack of fever, leukocytosis and bland CSF results, infectious aetiology was unlikely in this patient. Although his initial MRI findings were highly characteristic of changes seen with HSV encephalitis, his clinical presentation was not consistent with this diagnosis. Moreover, no other objective data supported HSV infection, as well as the lack of clinical improvement with intravenous acyclovir treatment.

Table 2 Serum autoimmune encephalitis panel results

Serum autoimmune encephalitis panel (ENCES)		
Result name	Result	Reference value
AChR (Muscle) Binding Ab	2.07 nmol/L	≤0.02
NMDA-R Ab CBA	Negative	Negative
VGKC Ab	0.00 nmol/L	≤0.02
LG11-IgG CBA	Negative	Negative
CASPR2-IgG CBA	Negative	Negative
GAD65 Ab Assay	0.00 nmol/L	≤0.02
GABA _B -R Ab CBA	Negative	Negative
AMPA-R Ab	Negative	Negative
ANNA-1	Negative	<1:240
ANNA-2	Negative	<1:240
ANNA-3	Negative	<1:240
AGNA-1	Negative	<1:240
PCA-1	Negative	<1:240
PCA-2	Negative	<1:240
PCA-Tr	Negative	<1:240
Amphiphysin Ab	Negative	<1:240
N-Type Calcium Channel Ab	0.00 nmol/L	≤0.03
P/Q-Type Calcium Channel Ab	0.00 nmol/L	≤0.02
AChR (Ganglionic Neuronal) Ab	0.00 nmol/L	≤0.02
CRMP-5-IgG	Negative	<1:240

AChR, acetylcholine receptor; AMPA, anti- α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; AGNA-1, anti-glia/neuronal antibody type 1; ANNA-1, antineuronal nuclear type 1 antibodies; ANNA-2, antineuronal nuclear type 2 antibodies; ANNA-3, antineuronal nuclear type 3 antibodies; CASPR2, contactin-associated protein 2; CBA, cell-based assay; CRMP-5-IgG, col lapsin response-mediator protein-5-IgG; CSF, cerebrospinal fluid; ENCES, encephalitis panel serum; GABA_B, gamma-aminobutyric acid-B; GAD65, glutamic acid decarboxylase 65; LG11, leucine-rich glioma inactivated 1; NMDA, anti-N-methyl-D-aspartate; PCA-1, Purkinje cell cytoplasmic type 1 antibodies; PCA-2, Purkinje cell cytoplasmic type 2 antibodies; PCA-Tr, Purkinje cell cytoplasmic type Tr antibodies; VGKC, voltage-gated potassium channel.

Vascular causes such as a stroke could present with neurological findings such as expressive aphasia, cognitive impairment, and have complications such as seizures. However, the time course and progressive development of his symptoms did not fit with the clinical presentation of a cerebrovascular accident and also essentially ruled out with MRI brain imaging.

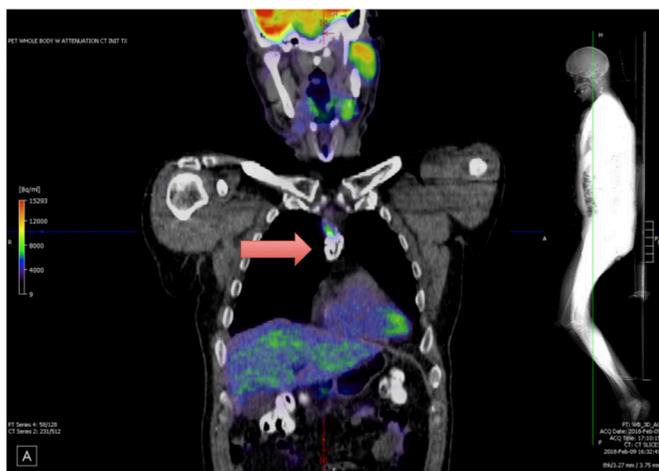


Figure 2 Coronal view of whole body PET/CT scan showing increased uptake in anterior mediastinum and a partially calcified 4.0×2.3×1.5 cm anterior mediastinal mass (shown by arrow).

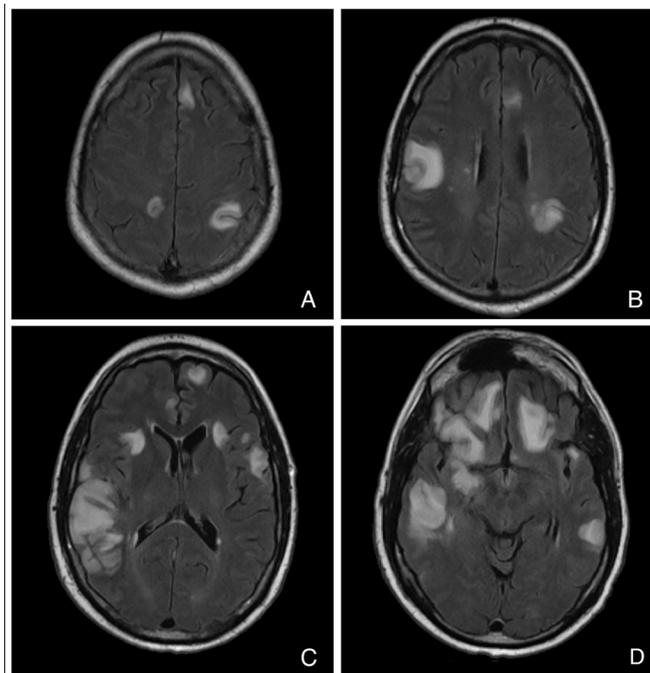


Figure 3 MRI brain T2-weighted/fluid-attenuated inversion recovery sequences shown with four axial views, advancing from superior to inferior from A to D. MRI obtained on second admission showing new areas of hyperintensities and inflammation.

Seizures can also present with acute onset of neurological deficits, but are usually more episodic and short lived without constant symptoms. Continuous electroencephalogram (EEG) was also performed on this patient that did not show any global epileptic activity, aside from the aforementioned PLEDs. Similarly, new onset primary psychiatric disorder did not fit this clinical picture in someone without prior personal or family history of any psychiatric disorders.

TREATMENT

After the discovery of the anterior mediastinal mass, thymoma and known associated paraneoplastic syndromes were considered. TAPE was thought to be the leading diagnosis that encompassed all of this patient's clinical presentation, supported by lab and imaging findings. The patient was started on intravenous immunoglobulin G (total dose of 2 g/kg, divided into 3 days), as well as high dose intravenous steroids (methylprednisolone 1000 mg for 5 days). His clinical status began to improve shortly thereafter. In addition, he underwent a successful video assisted thoracoscopic surgery for tumour resection, and pathology revealed the anterior mediastinal mass to be a type B2–B3 thymoma. Unfortunately, it is unclear if the thymoma tissue expressed muscle ACh receptors because further testing was not performed. He subsequently was discharged home with improving clinical symptoms and had close outpatient follow-up.

OUTCOME AND FOLLOW-UP

The patient underwent an MRI brain with and without contrast 1 month post-hospitalisation, which showed significant interval resolution of the previously described bilateral hemispheric cortically based lesions. Unfortunately, 3 months after the patient was discharged, he experienced a generalised tonic-clonic seizure that required re-hospitalisation. Repeat MRI on re-admission showed recurrence of multifocal bilateral T2/

FLAIR hyperintensities signifying widespread inflammation, notably in brand new areas when compared with his first admission's MRI (figure 3). The patient was again treated with high dose intravenous steroids (solumedrol 1g daily), but this time was also treated with plasma exchange (PLEX) therapy (which was thought to clear the autoantibodies quicker). The patient's clinical symptoms improved after steroid and PLEX therapies and was subsequently discharged home on a steroid taper (with oral prednisone), as well as levetiracetam 1500mg orally twice daily for seizure prophylaxis. Repeat MRI brain imaging 3 and 6 months status post his second admission showed interval resolution of the new brain lesions and his neurological status returned to baseline, with no further recurrences of disease to date.

DISCUSSION

Autoimmune or paraneoplastic causes of encephalitis are becoming more recognised, especially as laboratory testing for autoantibodies continue to advance. Recent literature reveals that these aetiologies of encephalitis are perhaps more common than previously thought.⁵ This is taking into account that refinement in immunohistochemistry, immunofluorescence assay and cell-based assay lab testing has made important recent diagnostic advancements in shedding light on autoantibody mediated encephalitis.

Although this patient was ultimately found to have muscle ACh receptor binding autoantibodies in both CSF and serum, positivity for this particular antibody is not specific and/or sufficient enough to be diagnostic of 'antibody positive' autoimmune encephalitis. In fact, it is important to acknowledge that muscle ACh receptor binding antibodies are not pathogenic to the CNS, and is not responsible for this patient's presenting encephalitis. Historically, neurologic symptoms found in the setting of positive antibodies to CASPR2 receptor or LGI1 were considered to be part of the 'classical' syndrome highly suggestive of limbic encephalitis.⁵ Ultimately, this patient's workup did not reveal positive results for any other autoantibody biomarkers, and the muscle ACh receptor antibodies were likely an incidental finding that fit with the discovery of his thymoma. The specific, autoimmune culprit responsible for his encephalitis remains unknown. However, given his clinical improvement with immunosuppressive therapy and tumour resection, we believe that his diagnosis is compatible with TAPE, despite not having a definitive autoantibody identified.

It is important to recognise that not all patients with autoimmune or paraneoplastic encephalitis have associated autoantibodies, and the lack of either serum or CSF autoantibodies does not exclude a potential autoimmune process. In all patients, consideration of alternative aetiologies is essential, as treatment decisions must often be made before imaging, EEG, or confirmatory antibody test results are available. Infectious aetiologies in particular should be excluded before initiating immunosuppressive therapies. In more than half of patients found to have paraneoplastic encephalitis syndromes, the neurologic symptoms on average preceded discovery of a tumour or cancer diagnosis by weeks to months. Therefore, there should be a low threshold to perform imaging for malignancy screening.⁶ The most frequent malignancies associated with paraneoplastic limbic encephalitis are lung cancer (usually small-cell lung cancer), seminoma and other testicular tumours, thymoma, breast cancer and Hodgkin's lymphoma.⁷ Prior literature reported association between limbic encephalitis due to thymoma and VGKC antibodies, but as more case reports come forth, the list of 'responsible' autoantibodies has continually developed to include even more different

biomarkers, as evidenced by the extensive list of antibodies tested in the expanded autoimmune encephalitis panel both in the serum and CSF for this patient.

In an effort to delineate the potential pathophysiology of autoimmune encephalitis, it has been proposed that preceding CNS infections can play a role in triggering autoimmune flares; however, this has only been demonstrated in limited case studies with HSV encephalitis. NMDA receptor antibody mediated encephalitis has been associated with the diagnosis and treatment of HSV encephalitis, with 20%–30% of patients who were NMDA receptor antibody-negative in serum and CSF at the time of HSV infection seroconverted to positive NMDA receptor antibodies in the setting of relapsing symptoms confirmed not to be from recurrent HSV infection.⁸ However, in this particular patient, it is unlikely that he had HSV infection triggering autoimmune encephalitis, as there was no confirmed evidence of CNS HSV infection, as well as alternative findings of a thymoma tumour.

Finally, it should be stressed that early consideration and recognition for autoimmune or paraneoplastic encephalitis is the only way to ensure prompt initiation of treatment. Early immunotherapy and cancer directed therapy (including tumour resection, if indicated) have been shown to have favourable outcomes, improved speed of neurological recovery, and reduced risk of relapses. Over 75% of patients with proper diagnosis and treatment had clinical resolution of neurological symptoms at 24 months from initial onset.⁹ Without treatment, progressive neurologic deterioration can occur over months to years, eventually resulting in death.

As our knowledge of antibody mediated autoimmune encephalitis continues to grow, we hope that emerging number of case reports, such as this one, contributes to our understanding of the diagnostic algorithms, treatment options and prognosis of this previously under-recognised aetiology of limbic encephalitis.

Learning points

- ▶ Although unusual, there are several case reports of thymoma associated paraneoplastic syndromes involving limbic or extralimbic areas of the central nervous system, rather than the peripheral nervous system as seen in myasthenia gravis associated with thymomas.
- ▶ Not all patients with autoimmune or paraneoplastic encephalitis have associated antibodies, and the lack of either serum or CSF autoantibodies does not exclude a potential autoimmune process.
- ▶ In greater than 50% of patients found to have paraneoplastic syndromes, the neurological symptoms precede discovery of a tumour or cancer diagnosis by weeks to months; therefore, there should be a low threshold to perform imaging for malignancy screening.
- ▶ There are rare cases of autoimmune encephalitis developing following HSV infections causing encephalitis, and prompt diagnosis and treatment with immunotherapy improves symptoms and outcomes.
- ▶ In paraneoplastic encephalitis, early immunotherapy and cancer directed therapy (including tumour resection, if indicated) have been shown to have favourable outcomes, improved speed of neurological recovery, and reduced risk of relapses.

Acknowledgements The authors would like to acknowledge the following individuals for their assistance in this case: Iris Ma, MD; Elizabeth Kim, MD, MS; and Glenn D. Egie, MD.

Contributors HL was the resident physician in charge of care for the patient during his hospitalisation. HL gathered all information including chart review, laboratory data and imaging. HL wrote the manuscript with support from RSE. RSE supervised the project.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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