Clinical Reasoning: A 59-Year-Old Man With Thymoma and Constitutional Symptoms, Seizures, and Multifocal CNS Lesions

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Abstract

A 59-year-old man first presented for an episode of left arm numbness. During workup, a thymoma was incidentally discovered and resected. The symptoms in his left arm were attributed to a cardiac pathology. One month later, he began to experience fatigue, weight loss, and anorexia, followed by one generalized tonic-clonic seizure. Workup including toxic and metabolic screening and MRI of the brain were unremarkable. He was started on an antiseizure medication and did well for 2 years, when his symptoms recurred. Repeat MRI of the brain showed multiple cortical T2-weighted fluid-attenuated inversion recovery (T2/FLAIR) hyperintense lesions without enhancement or diffusion restriction. Further workup included spinal MRI, CT of the chest/abdomen/pelvis, CSF studies, and autoimmune/paraneoplastic panels in CSF and serum, all of which were unremarkable. Serum testing was positive for striational antibodies, acetylcholine receptor (AChR)–binding antibodies, and AChR-modulating antibodies. He received high-dose steroids and plasma exchange with resolution of his symptoms and has since been stable on mycophenolate mofetil. This presentation highlights the rare association between thymoma and encephalitis. Prompt identification and treatment is critical. This article discusses the diagnostic approach to this rare presentation including essential features of the clinical presentation, appropriate workup, pertinent differential diagnoses, and key points for the treatment of these patients.

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Glossary

AChR = acetylcholine receptor; **GABA** = gamma-aminobutyric acid; **MOG** = myelin oligodendrocyte glycoprotein; **T2/FLAIR** = T2-weighted fluid-attenuated inversion recovery; **TAPE** = thymoma-associated paraneoplastic encephalitis

Section 1

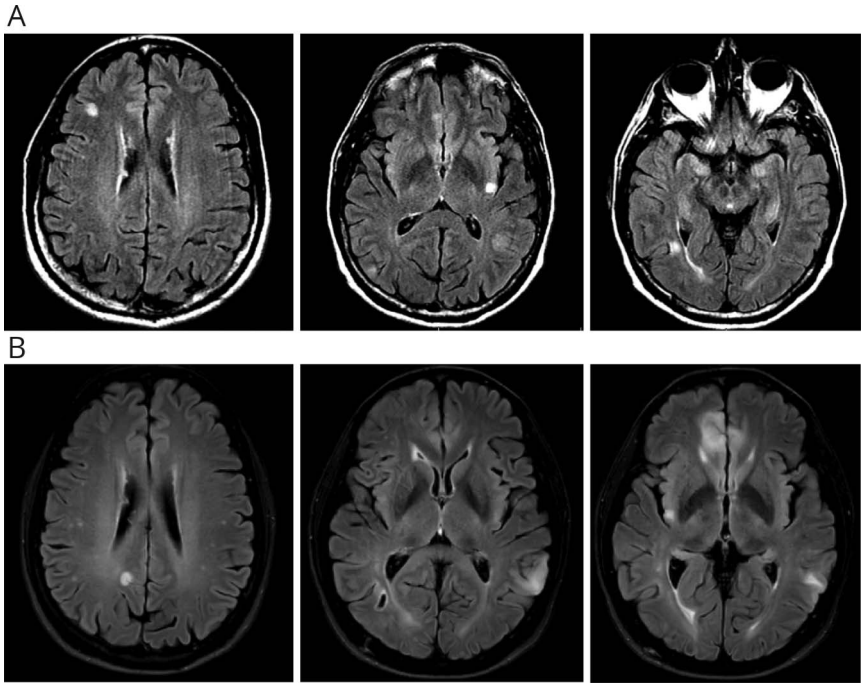
A 59-year-old man with no significant medical history first presented to a local emergency department after an episode of transient left arm numbness and chest pain. A CT of the chest identified an anterior mediastinal mass, which was confirmed to be a thymoma after resection. One month after surgery, he experienced one generalized tonic-clonic seizure and was started on levetiracetam. No cognitive symptoms were reported at this time. Evaluations including a basic metabolic panel and MRI of the brain were unremarkable, and repeat CT of the chest showed no recurrence of thymoma. He was later switched from levetiracetam to lamotrigine because of personality changes.

Two years after his initial presentation, he experienced another generalized tonic-clinic seizure and constitutional symptoms (fatigue, weight loss, and anorexia), followed by new cognitive complaints (such as difficulty remembering names) and irritability. He was admitted to an outside hospital for expedited workup. He was afebrile at presentation, and his initial neurologic examination was normal. MRI of the brain showed multiple cortical T2/FLAIR hyperintense lesions without enhancement or diffusion restriction (Figure, A).

Questions for Consideration:

1. What is the differential diagnosis for the presenting symptoms?
2. How do the MRI findings modify the differential?
3. What are the next steps in evaluation?

Figure Selected MRI Brain Sequences Obtained at Different Time Points



(A) MRI of the brain, selected axial T2 FLAIR sequences. There was no enhancement or diffusion restriction in other sequences (data not shown). For details see section 2. (B) MRI of the brain, selected axial T2 FLAIR sequences. For details see Section 3.

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Section 2

The differential diagnosis for the patient's symptoms and radiologic findings is broad. The history of thymoma raises the possibility of a paraneoplastic disorder or tumor progression. Demyelinating disorders, such as multiple sclerosis, neuromyelitis optica spectrum disorders, and myelin oligodendrocyte glycoprotein (MOG)–associated disease, should be high on the differential diagnosis, although the radiologic features and clinical presentation are not typical for multiple sclerosis. Thymomas are associated with immunodeficiencies and hypogammaglobulinemia (Good syndrome), which increase the risk of opportunistic infections and autoimmunity. Stroke or a malignancy should also be considered in an adult older than age 50 years. The MRI imaging showing multifocal T2/FLAIR hyperintense lesions without contrast enhancement or diffusion restriction helps narrow the differential diagnosis, specifically making stroke and metastasis far less likely. The lack of fever or other systemic infectious signs lowers the suspicion for infectious etiologies, although selected infections such as progressive multifocal leukoencephalopathy should be considered given the imaging findings. Rheumatologic disorders such as systemic lupus erythematosus and Sjögren syndrome may present with nervous system involvement but would typically present with other systemic signs and symptoms. Paraneoplastic syndromes are common in patients with a history of thymoma and are therefore high on the differential.

The patient underwent further workup at an outside hospital; spinal MRI and CT of the chest, abdomen, and pelvis were unrevealing. Full-body PET scan was notable for an 11-mm thyroid nodule, which was confirmed to be a benign adenoma after biopsy. His CSF profile was noninflammatory, with unremarkable infectious, autoimmune, and paraneoplastic studies. Serum testing was positive for striational antibodies (1:15,360), acetylcholine receptor (AChR)–binding antibodies (1.93 nmol/L), and AChR-modulating antibodies (33% inhibition). The patient denied current and historical symptoms of neuromuscular junction dysfunction. He underwent brain biopsy, which was nondiagnostic showing reactive gliosis and rare, atypical glial cells. He was started on dexamethasone 4 mg daily after biopsy by his outside provider and noted improvement of his symptoms.

Questions for Consideration:

1. How does this information change the differential diagnosis?
2. What is the significance of striational, AChR-binding, and AChR-modulating antibodies in this context?

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Section 3

The workup ruled out a relapse of his thymoma, new malignant process, and infection. Striational, AChR-binding and AChR-modulating antibodies can be associated with neuromuscular junction disorders, however are not associated with central nervous system autoimmunity. Their presence suggests a loss of self-tolerance leading to the generation of autoantibodies frequently seen in patients with thymoma. Our patient did not have any symptoms suggestive for a neuromuscular junction disorder such as myasthenia gravis, and the antibodies were therefore not pathogenic. Although antibodies associated with autoimmune encephalitis were negative in serum and CSF testing, the diagnosis of autoimmune encephalitis can be made in their absence.[1]

Repeat MRI of the brain after 3 weeks of dexamethasone showed worsening of T2/FLAIR hyperintense lesions (Figure, B). He was referred to our center for expedited workup and underwent repeat lumbar puncture; basic indices, IgG index, and oligoclonal bands were within normal limits. Testing for autoantibodies was expanded to include aquaporin-4, MOG, gamma-aminobutyric acid (GABA) A, and other antibodies in serum and CSF (see Table for a selection of antibodies tested in this case), which all returned negative. Based on his clinical presentation, he was diagnosed with thymoma-associated paraneoplastic encephalitis (TAPE). He subsequently received treatment with 5 days of intravenous methylprednisolone, followed by 5 sessions of plasma exchange. He showed marked clinical improvement after plasma exchange. He was started on long-term immunosuppression with mycophenolate mofetil with complete resolution of his cognitive symptoms and seizures; at his 4-month follow-up, he continues to be stable on this regimen. Repeat MRI of the brain 5 months after high-dose steroids and plasma exchange showed almost complete resolution of the T2/FLAIR hyperintense lesions.

Discussion

Approximately 50% of patients with thymoma develop a paraneoplastic syndrome.[2,3] Myasthenia gravis is the most common thymoma-associated disorder, occurring in 24.5%—40% of all patients with thymoma.[4] TAPE is a rare entity that can present with variable clinical presentations, antibody findings, and MRI features.[2,5,6] A recent case series included 43 cases with a median age at onset of 52 years and a slight female predominance (60%).[6] The thymoma was either locally invasive or metastatic in 51% of cases and preceded the diagnosis of encephalitis in 37% of cases.[6] With timely treatment of thymoma and initiation of immunotherapy, most patients have a good functional outcome.[6]

Patients with thymoma can present with a variety of autoantibodies to nervous system antigens. Antibodies associated with myasthenia gravis are most commonly detected and may be present in patients without features of a neuromuscular junction disorder.[7] AChR antibodies are frequently found in patients with TAPE but do not necessarily play a pathogenic role. Neuronal surface antibodies associated with autoimmune encephalitis (NMDAR, AMPAR, LGI1, CASPR2, GABA A/B R, see Table) are commonly seen in TAPE, but their presence is not required to make the diagnosis.[6,8-10] Intracellular antibodies such as CRMP5, GAD-65, and ANNA-1 can also be detected.[6] Multiple autoantibodies may be identified concomitantly because of a loss of normal thymic function and dysregulation of B-cell function.[11-13] When multiple neuronal antibodies are detected, the probability of

Table Selection of Antibodies Associated With Autoimmune Conditions Including Autoimmune Encephalitis and Paraneoplastic Syndromes Tested for This Patient

Antigen (antibody) name	Abbreviation	Serum	CSF	Clinical features of encephalitis	Other possible clinical features
Antibodies associated with encephalitis					
N-methyl-D-aspartate receptor[4,15]	NMDAR	Negative	Negative	Psychosis, behavioral changes	Hyperkinetic movements, dysautonomia
Gamma-aminobutyric acid A receptor[1,5,15]	GABA A R	Negative	Negative	Behavioral and cognitive changes, seizures	—
Gamma-aminobutyric acid B receptor[1,15]	GABA B R	Negative	Negative	Limbic encephalitis with prominent seizures	—
α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor[1,15]	AMPAR	Negative	Negative	Limbic encephalitis	—
Collapsin response mediator protein 5[15]	CRMP5, CV2	Negative	Negative	Limbic encephalitis	Encephalomyelitis, cerebellar degeneration, neuropathy/neuronopathy, gastrointestinal pseudo-obstruction

Continued

Table Selection of Antibodies Associated With Autoimmune Conditions Including Autoimmune Encephalitis and Paraneoplastic Syndromes Tested for This Patient *(continued)*

Antigen (antibody) name	Abbreviation	Serum	CSF	Clinical features of encephalitis	Other possible clinical features
Antineuronal nuclear antibody, type 1[4,15]	ANNA-1, Hu	Negative	Negative	Limbic encephalitis	Encephalomyelitis, cerebellar degeneration, neuropathy/neuronopathy, gastrointestinal pseudo-obstruction
Antineuronal nuclear antibody, type 2[15]	ANNA-2, Ri	Negative	Negative	Brainstem encephalitis	—
Leucine-rich glioma inactivated 1[4,15]	LGI1	Negative	Negative	Limbic encephalitis with characteristic faciobrachial dystonic seizures	Hyponatremia
Contactin-associated protein-like-2[4,15]	CASPR2	Negative	Negative	Limbic encephalitis Morvan syndrome	Acquired neuromyotonia
Dipeptidyl-peptidase-like protein 6[15]	DPPX	Negative	Negative	Encephalitis	PERM, CNS hyperexcitability, weight loss, diarrhea
Myelin oligodendrocyte glycoprotein[1,15]	MOG	Negative	NA	Unihemispheric cortical encephalitis with seizures, ADEM[1]	Optic neuritis, myelitis
Glutamic acid decarboxylase 65[4,15]	GAD-65	Negative	Negative	Limbic encephalitis, chronic epilepsy	Stiff person syndrome, cerebellar degeneration[4]
Glial fibrillary acidic protein[15]	GFAP	Negative	Negative	Meningoencephalitis	—

Antigen (antibody) name	Abbreviation	Serum	CSF	Common clinical presentation
Other Antibodies Included in Testing				
Amphiphysin[15]	—	Negative	Negative	PERM, neuropathy/neuronopathy, encephalomyelitis
Metabotropic glutamate receptor, type 1[15]	mGluR1	Negative	Negative	Cerebellar ataxia
Purkinje cell cytoplasmic antibody, type 1[15]	PCA-1	Negative	Negative	Rapidly progressive cerebellar syndrome
Purkinje cell cytoplasmic antibody, type 2[15]	PCA-2	Negative	Negative	Sensorimotor neuropathy, rapid progressive cerebellar syndrome, encephalomyelitis
Purkinje cell cytoplasmic antibody, type Tr[15]	PCA-Tr	Negative	Negative	Rapidly progressive cerebellar syndrome
Aquaporin 4[1]	AQP4	Negative	NA	Neuromyelitis optica
P/Q voltage-gated calcium channel[4,15]	VGCC	Negative	NA	Lambert Eaton syndrome
N-type calcium channel[11]	—	Negative	NA	Myasthenia gravis
Alpha 3-ganglionic acetylcholine receptor[4]	gAChR	Negative	NA	Autonomic neuropathy
Neuronal (V-G) K channel[4]	—	Negative	NA	Acquired neuromyotonia
Striational[4,11]	—	**Positive**	NA	Myasthenia gravis
Acetylcholine receptor binding[7,11]	AChR	**Positive**	NA	Myasthenia gravis
Acetylcholine receptor modulating[7,11]	AChR	**Positive**	NA	Myasthenia gravis
Thyroid peroxidase[1]	TPO	Negative	NA	Confusion, psychosis, Hashimoto encephalopathy
Antiglial neuronal nuclear antibody 1[10,15]	AGNA-1, SOX-1	Negative	Negative	Lambert Eaton syndrome, cerebellar degeneration

GABA = gamma-aminobutyric acid; MOG = myelin oligodendrocyte glycoprotein; NA = not applicable (not tested); PERM = Progressive encephalomyelitis with rigidity and myoclonus; SLE = systemic lupus erythematosus.
Antibodies with positive results in this patient are highlighted in bold. For a detailed overview on antibody mediated syndromes see references by Evoli et al. and Graus et al.[1,4,15] GABA A receptor antibody testing was performed by Dr. Eric Lancaster at University of Pennsylvania. A complete list of antibodies tested for this patient is available upon request from the authors.

an occult thymoma increases, and malignancy screening is strongly recommended.[14]

The clinical manifestation and imaging findings of TAPE can vary widely. The most common presentation is associated with multiple T2 FLAIR hyperintense lesions on MRI of the brain as presented in this case.[6,10] Among these patients, GABA A R antibodies are most frequently found, and a majority of the GABA A R antibody–positive patients developed seizures, cognitive impairment, and/or behavioral changes.[6] Other clinical presentations include encephalitis with peripheral nerve hyperexcitability (CASPR2 antibody predominant), limbic encephalitis, and progressive encephalomyelitis with rigidity and myoclonus (associated with glycine receptor antibodies).[5,6,10] MRI-negative cases of TAPE have been described as well.[6,10]

If there is suspicion for TAPE, diagnostic workup with MRI of the brain, whole-body tumor screening (CT, followed by PET-CT), CSF studies, and antibody testing in serum and CSF should be initiated without delay. Brain biopsy is sometimes performed, but the yield is low because it usually shows nonspecific lymphocyte and plasma cell infiltration.[10] Differential diagnoses including infections, metastasis, and primary brain tumors should be considered during workup. Once the diagnosis is established, rapid initiation of immunotherapy (high-dose steroids, intravenous immunoglobulins, and/or plasma exchange) with tumor resection determine the survival, as well as functional and cognitive outcomes, in these patients. Antibody titers decrease after tumor resection and complete tumor resection increases the chance for TAPE resolution and symptom-free survival.[2,10] Therefore, prompt identification and treatment of TAPE is crucial.

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