A 45-year-old woman presented with subacute memory loss, confabulation, and behavioral changes. Eight years earlier she was diagnosed with myasthenia gravis (MG) associated with type B2 thymoma, which was treated with surgery and radiation therapy. Four years later, she developed retroperitoneal and mediastinal metastases that were surgically removed. In addition, she had well-controlled epilepsy since childhood and had been asymptomatic on phenobarbital, pyridostigmine, prednisone, and azathioprine.

On examination, she was disoriented to time and space, showed impaired memory with confabulations, demonstrated mild executive dysfunction, and had a Mini-Mental State Examination (MMSE) score of 20. The remainder of the neurologic and physical examination was unremarkable. Brain MRI showed multiple cortical and subcortical T2/FLAIR hyperintense non-contrast-enhancing lesions with extensive mesial temporal lobe involvement that was worse on the right side (figure 1). CSF was normal. EEG showed periodic lateralized epileptiform discharges (PLEDs) in the right temporal region and left temporal onset electroencephalographic seizures without clinical manifestations. Brain fluorodeoxyglucose (FDG) PET showed uptake in the right insular and temporal regions. Whole-body FDG-PET disclosed a hypermetabolic pleural lesion. Additional laboratory tests showed moderately increased C-reactive protein (33.3 mg/dL) and erythrocyte sedimentation rate (28 mm), and positive acetylcholine receptor, antinuclear antibody, and double-stranded DNA antibodies. Thyroid and GAD65 antibodies were negative.

Methylprednisolone 1 g per day for 5 days was started, followed by 6 plasma exchange sessions. After treatment, she scored 25 points on the MMSE, and her memory and anxiety improved. Follow-up brain MRI showed substantial reduction in the number and size of all abnormalities, mainly in the temporal lobes (figure 1), and the PLEDs resolved. Antibodies against cell surface or synaptic proteins were assessed in serum and CSF obtained before immunotherapy using rat brain immunohistochemistry and cell-based assays, as reported. These studies showed high levels of serum (1:320) and CSF (1:80) antibodies against the GABA<sub>A</sub> receptor and low levels of antibodies against LGI1 (serum 1:80, CSF 1:20). Antibodies against GABA<sub>B</sub> receptor, AMPA receptor, NMDA receptor, Caspr2, GlyR, mGLUR5, and mGLUR1 were negative.

Three months after discharge, the patient was having a good recovery, but the brain MRI showed a new subcortical lesion in the right frontal lobe. She underwent repeat methylprednisolone and plasma exchange and surgical removal of the pleural lesion, whose pathology was consistent with thymoma. Tumor antigen expression was examined in tissue obtained from the first thymoma resection (8 years earlier), which showed lack of GABA<sub>A</sub> receptor and LGI1 reactivity (not shown), and in tissue from the pleural lesion, which showed expression of both antigens (figure 2). After the indicated treatment, the patient’s neurologic function returned close to baseline, and a repeat brain MRI showed resolution of all lesions.

Discussion. Although thymoma is frequently associated with autoimmune disorders, the most common being MG,<sup>3</sup> encephalitis associated with thymoma is rare. A review of the literature demonstrates 30 previously reported cases (table e-1 at Neurology.org/nn).
These patients often developed clinical features of limbic dysfunction and coexistence of other autoimmunities, similar to the case reported here, but the target antigens were largely unknown. After the initial description of anti-GABA<sub>A</sub> receptor encephalitis, Ohkawa et al. reported 2 cases with anti-GABA<sub>A</sub> receptor encephalitis and thymoma. These 2 patients had been previously reported as having limbic encephalitis associated with VGKC antibodies and shared similarities with our patient, including subacute onset of cognitive and memory deficits associated with thymoma recurrence or residual thymoma, coexistence of LGI1 or Caspr2 antibodies with GABA<sub>A</sub> receptor antibody, and remarkable brain MRI abnormalities, which are strikingly similar to those reported in other patients with GABA<sub>A</sub> receptor encephalitis.

Our patient provides 2 novelties: First, high levels of GABA<sub>A</sub> receptor antibodies were found both in serum and CSF; In the above-mentioned 2 cases with thymoma, the antibody testing was performed only in serum. Second, to our knowledge, this is the
first case in which expression of the GABA<sub>A</sub> receptor is demonstrated in the tumor. It is interesting that this receptor and LGI1 were not detected in the initial sample of tumor obtained 8 years earlier but were present in the most recent sample. These findings raise the question of whether thymoma could express different antigens during its progression, leading to manifestations of different paraneoplastic diseases, as occurred in our and other cases of thymoma-associated encephalitis.5–7

This report emphasizes the importance of aggressive immunotherapy along with surgical removal of the tumor in the category of disorders associated with antibodies against relevant cell surface antigens (GABA<sub>A</sub> receptor, LGI1), which in our case resulted in clinical and radiologic improvement. This is in contrast with the previously reported patient, who was treated with immunotherapy but did not have tumor removal and had persistent severe cognitive deficits.5,6

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Figure 2  Expression of GABA<sub>A</sub> receptor and LGI1 by patient’s thymoma

Tissue sections of the patient’s thymoma incubated with biotinylated immunoglobulin G (IgG) from a patient with only GABA<sub>A</sub> receptor antibodies (A), another patient with only LGI1 antibodies (C), and a control subject without antibodies (E) compared with the reactivity of a commercial antibody against GABA<sub>A</sub> receptor (B) (rabbit polyclonal anti-a1 GABA<sub>A</sub> receptor, abcam, ab33299, diluted 1:50), a commercial antibody against LGI1 (D) (rabbit polyclonal anti-LGI1, abcam, ab30868, diluted 1:50), and the secondary antibody alone (F). Note the similar pattern of reactivity of human antibodies and commercial antibodies, indicating that the tumor expresses epitopes of GABA<sub>A</sub> receptor and LGI1 proteins. The dilution of human IgG was 1:50. All sections were mildly counterstained with hematoxylin.
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GABA_A receptor and LGI1 antibody encephalitis in a patient with thymoma

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