Multifocal Paraneoplastic Cortical Encephalitis Associated With Myasthenia Gravis and Thymoma

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Objectives: To report a case of multifocal cortical encephalitis associated with thymoma and to establish an association of this thymoma-related paraneoplastic syndrome with voltage-gated potassium channel antibodies.

Design: Case report.

Setting: University hospital.

Patient: A 43-year-old woman with a history of seropositive myasthenia gravis and successfully treated invasive thymoma. Four years after thymectomy, she presented with seizure and rapidly progressive confusion and aphasia. Myasthenia gravis remained in pharmacological remission. Magnetic resonance imaging of the brain showed innumerable cortically based signal abnormalities as well as extensive left mesial temporal lobe abnormality with minimal enhancement.

Results: Chest computed tomography showed abnormal pleural thickening of the left lung, which proved to be recurrent metastatic thymoma. Results of serological evaluation were positive for acetylcholine receptor, striatal, and voltage-gated potassium channel antibodies. She showed partial improvement in response to immunotherapy and chemotherapy but ultimately died 2 months later of tumor complications.

Conclusions: Thymoma and myasthenia gravis may be associated with other autoimmune neurological disorders including paraneoplastic encephalitis. This second case of thymoma-associated multifocal cortical encephalitis demonstrates that autoimmune encephalitis can extend to cortical regions outside the limbic system. Autoimmune encephalitis should be considered in the differential diagnosis of patients with myasthenia gravis or thymoma who develop new cognitive symptoms.

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A 43-YEAR-OLD RIGHT-HANDED woman had a history of seropositive myasthenia gravis (MG) and invasive thymoma (stage IV) diagnosed in 2002. Her initial symptoms were fatigable weakness, dysarthria, diplopia, and ptosis. At that time, she underwent thymectomy followed by radiation therapy. She was treated with 500 mg of mycophenolate mofetil twice a day, and her symptoms improved. Myasthenia gravis was considered to be in pharmacological remission. Four years after thymectomy, she had a single unexplained seizure and started taking phenytoin. Six months after the seizure, she began complaining of intermittent nausea and vomiting and then, over a period of 1 week, she became confused and progressed rapidly to complete mutism. She presented to a local hospital. Cerebrospinal fluid analysis showed lymphocytic pleocytosis (70 cells) and elevated protein level (101 mg/dL) with a normal glucose level. Treatment with acyclovir was initiated, but she did not improve. Results of cerebrospinal fluid cultures and polymerase chain reaction analysis for herpes simplex virus and West Nile virus were negative.

She was transferred to our institution for further management. On presentation, she was awake and alert but did not speak. She appeared to be in no distress and was afibrile. She could not follow spoken commands but would attend to sounds. She would imitate gestures and could participate in the neurological examination. Strength and tendon reflexes were normal. There was no ocular or bulbar weakness; she was judged to be globally aphasic rather than anarthric. Magnetic resonance imaging of the brain showed innumerable cortically based signal abnormalities as well as extensive left mesial temporal lobe abnormality with minimal enhancement (Figure 1). Results of additional laboratory work were normal or negative, including erythrocyte sedimentation rate, antinuclear antibody titer, angiotensin-converting enzyme test, and serological tests for Lyme disease, syphilis, human immunodefi-
ciency virus, fungi, toxoplasmosis, and West Nile virus. The complete blood cell count and CD4 T-cell count were normal. Thyroid function was normal, and results of a thyroperoxidase antibody test were negative.

Electroencephalogram showed intermittent periodic lateralized epileptiform discharges in the left temporal region as well as electrographic seizures that appeared to arise independently from both temporal lobes. Sero-

logical studies were positive for markers of MG including acetylcholine receptor binding antibody (1.45 nmol/L), acetylcholine receptor modulating antibody (100%), and striational antibodies (1:15360). Voltage-gated potassium channel antibodies were also detected (0.45 nmol/L, normal <0.02 nmol/L). The rest of the paraneo-

plastic antibody profile was negative, including collapsin response-mediator protein 5 antibodies.

Computed tomography of the chest with contrast was performed to assess for malignancy. This showed bands of abnormal pleural thickening at the left lung base consistent with metastatic thymoma. A computed tomography–guided pleural biopsy showed a mixture of mature lymphocytes and epithelial components consistent with type B2 thymoma (Figure 2).

She received treatment with anticonvulsants, high-
dose intravenous methylprednisone (1 g daily for 5 days), and intravenous immunoglobulin (2 g/kg divided over another 5 days). She was then transferred to a cancer center, where she received 1 cycle of chemotherapy. There was some improvement of cognitive function and speech returned, but she ultimately died 2 months later of medical complications of her chest malignancy.

COMMENT

Thymoma is frequently associated with autoimmune dis-

orders. About 15% of patients with MG have thymoma.1 Thymoma and MG may be associated with other autoimmune neurological disorders including paraneoplastic encephalitis.1,3 Our patient had evidence of a multifocal cortical encephalitis as well as typical radiographic features of paraneoplastic limbic encephalitis involving the left mesial temporal lobe. Her most prominent pre-

Figure 1. Magnetic resonance and computed tomographic images. A-D, Axial fluid-attenuated inversion recovery images showed numerous cortically based signal abnormalities. There was extensive involvement of the left mesial temporal lobe (C) (arrow) and complete sparing of the cerebellum (D). E and F, Coronal T1-weighted images after administration of gadolinium showed minimal enhancement of the left mesial temporal lobe (E) (arrow) and the large left parietal lesion (F) (arrow). The rest of the cortical lesions showed no contrast enhancement. G, Contrast-enhanced computed tomography of the chest showed abnormal pleural thickening (arrow) of the posterior left lung base consistent with metastatic thymoma.

Figure 2. Computed tomography–guided pleural biopsy showing a mixture of mature lymphocytes (small blue cells) and epithelial components (larger, pale cells) consistent with type B2 thymoma (hematoxylin-eosin, original magnification ×100).
senting symptom of severe global aphasia corresponds anatomically to involvement of the dominant frontal and temporal cortex, which was significantly involved on the magnetic resonance images and electroencephalography. This encephalitic presentation occurred in the absence of any clinical signs of worsening MG. Investigation confirmed recurrent invasive thymoma. She responded partially to intravenous immunoglobulin and chemotherapy.

There are a few previous reports of thymoma-associated paraneoplastic encephalitis with variable responses to immunomodulatory treatment. This case further establishes that autoimmune encephalitis can occur as a paraneoplastic consequence of thymoma. Most examples of paraneoplastic encephalitis involve the limbic system and related structures. To our knowledge, this is only the second case with a unique pattern of multifocal cortical involvement associated with thymoma. Potassium channel antibodies were found in this case while collapsin response-mediator protein 5 antibodies were found in the previously reported case.8 The previously reported case showed a good response to plasma exchange after other therapies failed.

Antibodies against voltage-gated potassium channels have clearly been associated with thymoma and with paraneoplastic and autoimmune forms of limbic encephalitis.9,10 These antibodies have also been associated with autonomic disturbances affecting gastrointestinal motility.11,12 All of our patient’s symptoms (nausea and vomiting, seizures and encephalitis) fit within the voltage-gated potassium channel antibody clinical spectrum. Other autoantibodies typical of paraneoplastic limbic encephalitis in the context of small-cell lung carcinoma, such as antineuronal nuclear autoantibody type 1, were not found. Acetylcholine receptor binding and modulating antibodies and striatal antibodies were also detected in this patient to support the diagnosis of paraneoplastic autoimmunity in the setting of thymoma.

This case emphasizes the importance of considering paraneoplastic encephalitis associated with thymoma in the differential diagnosis of patients with MG who develop new cognitive symptoms. It also emphasizes the importance of investigating for recurrent malignancy in a patient with a known history of cancer who develops new neurological symptoms. Antibody markers can help confirm the suspicion of a paraneoplastic cause and direct the search for cancer. The role of intravenous immunoglobulin or other immunomodulatory treatments in thymoma-associated encephalitis needs further evaluation.

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REFERENCES: