Thymoma-associated paraneoplastic encephalitis (TAPE): Diagnosis and treatment of a potentially fatal condition

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Up to 50% of patients with thymoma have paraneoplastic neurologic syndromes, the most common being myasthenia gravis.¹ There are rare case reports of thymoma-associated paraneoplastic limbic or extralimbic encephalitis that can lead to progressive neurologic decline and death without treatment. We report a case of a malignant thymoma presenting as paraneoplastic encephalitis and review the clinical characteristics, treatments used, and outcome of 28 patients with this disorder published according to a PubMed and MEDLINE search (1950–2010).

CLINICAL SUMMARY

A previously asymptomatic 61-year-old woman had generalized intractable seizures. Brain magnetic resonance imaging (MRI) showed bilateral foci of cortical and subcortical nonenhancing signal abnormalities on T₂-weighted images (Figure 1, A). Chest computed tomography (CT) revealed a large anterior mediastinal mass (Figure 1, C) that, on biopsy, showed malignant thymoma. Analysis of cerebrospinal fluid detected a predominantly lymphocytic pleocytosis and positive LGI1 antibodies (previously known as voltage-gated potassium channel antibodies).²

The patient received anticonvulsants, human intravenous immunoglobulin G (IgG) (400 g/kg daily), and corticosteroids (methylprednisolone 1 gm daily) for 5 days plus a prednisone taper with resolution of neurologic symptoms. Four weeks later, the patient underwent complete, en bloc resection of the mediastinal mass that was invading through the pericardium (type B3, World Health Organization classification, Masaoka stage III). She received adjuvant radiation therapy (5040 cGy) owing to suspected invasion into the pericardial space. Four weeks later, brain MRI showed

FIGURE 1. A, MRI of the head at presentation. White arrows show some of the bilateral lesions. B, MRI of the head 3 months later, after immunotherapy and surgery. C, Coronal CT of the chest showing malignant thymoma invading the innominate vein. D, Coronal CT of the chest 6 month after surgery showing no residual disease. *MRI*, Magnetic resonance image; *CT*, computed tomogram.

decrease in size of the brain lesions (Figure 1, B). Two years after the operation, the patient has no evidence of tumor recurrence (Figure 1, D) or neurologic impairment.

DISCUSSION

Since 1988, when the first case of paraneoplastic encephalitis in the setting of thymic cancer was reported, 28 cases of thymoma-associated paraneoplastic encephalitis (TAPE) have been described (Table 1). The encephalitis can be confined to the limbic system or multifocal and extralimbic, as in our case. In most patients (82%), neurologic manifestations include memory loss, confusion, and seizures. Seventy percent exhibited bilateral foci of nonenhancing hyperintensity on brain MRI, some appearing weeks after onset of symptoms. The differential diagnosis includes metastases, primary brain tumors, and infection. The presence of a mediastinal mass and pathologic confirmation of

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TABLE 1. Clinical features of thymoma-associated paraneoplastic encephalitis

Author	Age/sex	Symptoms	Stage	MRI, T ₂ -weighted	Pleocytosis	Antineuronal antibodies	Treatment	Outcome
McArdle (1988)	41/M	Confusion, memory deficit, hallucinations	III		No	ANA (serum) oligoclonal IgG bands (CSF)	Partial thymectomy, radiation, corticosteroids	Death (1 mo)
Ingenito (1990)	59/M	Confusion, memory deficit, hypersomnolence	I	Normal	13 WBC		Corticosteroids	Death (51 d)
Cunningham (1994)	56/F	Confusion, memory deficit, emotional lability	IVA	Initially normal, subsequent left temporal lobe lesions			Thymectomy, radiation, chemotherapy	No residual symptoms
Antoine (1995)	58/F	Visual and auditory hallucinations, confusion	III	Hyperintensity in right hippocampus	Yes	Antineuronal cytoplasmic (serum and CSF)	Thymectomy, radiation	No residual symptoms
Antoine (1995)	67/F	Confusion, agitation, memory deficit, hallucinations	II	Hyperintensity on right	No	Antineuronal nuclear (serum only, CSF did not react)	Thymectomy, radiation	Mild memory deficit
Evoli (1999)	32/M	Confusion, memory deficit, seizures	III	Hyperintensity and edema of bilateral hippocampi	25 WBC		Thymectomy, radiation, chemotherapy, corticosteroids, plasmapheresis	Mild memory deficit, dependent on corticosteroids
Rickman (2000)	55/M	Malaise, dysarthria, aphasia, seizures	II*	Bilateral hyperintensity	Yes	AChR, CRMP5 (serum)	Partial thymectomy, corticosteroids, plasmapheresis	Residual symptoms
D'Avino (2001)	61/M	Confusion, memory deficit, irritable, hallucinations	III	Normal		Antibody reactivity to Perkinje cells (serum and CSF)	Thymectomy, radiation	Mild memory deficit
Fujii (2001)	55/M	Confusion, memory deficit, irritable, mania, seizures	I*	Bilateral high intensity	No	At autopsy, hippocampus showing anti-human IgG	Thymectomy	Death (4 mo)
Vernino (2002)	66/F	Hoarseness, unilateral loss of hearing, areflexia	III			ANNA-1, VGCC (serum)	Partial thymectomy, Chemotherapy	Death (7 mo)
Vernino (2002)	34/M	Dysarthria, dysphagia	II	Normal	10 WBC	AChR, ANNA-1 (serum)	Thymectomy, corticosteroids, plasmapheresis	Residual symptoms, memory deficit, labile personality
Vernino (2002)	34/F	Vertigo, tinnitus, vomiting	I	Normal, 2.5 mo later bilateral cortical lesions		ANNA-1, VGKC (serum)	Thymectomy	Residual symptoms, fixed right pupil
Vernino (2002)	39/F	Dysphagia, weakness	III	Normal		ACHR, ANNA-1, CRMP-5 (serum)	Partial thymectomy, radiation, chemotherapy, corticosteroids, plasmapheresis	Not reported
Ances (2005)	44/F	Confusion, memory deficit, combativeness	II	Initially normal but 5 d later bilateral temporal, cerebellar lesions	Yes	Neuropil reactivity (serum and CSF)	Thymectomy, corticosteroids, IgG	No residual symptoms
Ances (2005)	38/M	Confusion, memory deficit, agitation, seizures	III	Bilateral nonenhancing lesions	7 WBC	Neuropil and GAD (serum and CSF)	Thymectomy, corticosteroids, IgG, plasmapheresis	Memory deficit, gait difficulty, dependent on corticosteroids
Chaudhry (2007)	62/F	Memory deficit, cognitive impairment	IVA	Bilateral hippocampal hyperintensity			Thymectomy, chemotherapy, rituimab monoclonal antibody, plasmapheresis	Progressive cognitive deficit

(Continued)

TABLE 1. Continued

Author	Age/sex	Symptoms	Stage	MRI, T ₂ -weighted	Pleocytosis	Antineuronal antibodies	Treatment	Outcome
Evoli (2007)		Limbic encephalitis	B2					
Khella (2007)	41/F	Ataxia, dysarthria, dementia	I	Bilateral hyperintensity	Yes	NMDAR/VGKC (serum and CSF)	Corticosteroids, IgG, plasmapheresis	Death (31 mo)
Gesundheit (2008)	28/M	Auditory and visual hallucinations, incoherent speech	B2/II	Subtle hyperintensity of temporal lobes			Thymectomy, IgG	No residual symptoms
Graus (2008)	44/F	Behavior change, confusion	I*	Not done	Yes	CV2 (CRMP5) (serum and CSF)		Death (2 wk)
Lai (2009)	44/F	Memory deficit, confusion, seizure, combativeness	II*	Normal, 5 d later increased temporal lobe signal	44 WBC	GluR2, ANA, dsDNA, cardiolipin (serum and CSF)	Thymectomy, IgG, corticosteroids, azathioprine	Residual short-term memory deficit
Lai (2009)	38/M	Memory deficit, confusion, seizure, agitation, perseveration	II*	Bilateral hyperintense lesions	7 WBC	GluR2, GAD (serum and CSF)	Thymectomy, radiation, corticosteroids, IgG, plasmapheresis	Residual short-term memory deficit, steroid-dependent muscle spasms and rigidity
Lai (2009)	44/F	Confusion, behavioral change, gait unsteadiness, progressive unresponsiveness	I*	Normal	15 WBC	GluR2, GluR1, CV2 (CRMP5) (serum and CSF)	None, diagnosed at autopsy	Death (24 mo)
Hammond (2009)	43/F	Seizure, confusion	B2/II	Minimally enhancing bilateral lesions	Yes	AchR, VGKC (serum)	Thymectomy, radiation, chemotherapy, corticosteroids, IgG	Death (2 mo)
Monstad (2009)	49/F	Memory deficit	I	Bilateral hippocampal lesions	10 WBC	CRMP5, AchR (serum)	Thymectomy, corticosteroids, plasmapheresis	Memory deficit
Rizzardi (2009)	55/F	Seizure, aphasia	B/II	Multiple, bilateral lesions of insular, parietal, and temporal lobes		Normal autoimmune serologic exam	Thymectomy, radiation therapy	No residual symptoms and disease free
Werry (2009)	32/M	Vertigo, diplopia, ataxia, myoclonic jerking	B1/I	Normal, 1 mo later bilateral cortical nonenhancing hyperintensity	Mild increase	CV2/CRMP-5 (serum)	Thymectomy, corticosteroids, IgG, plasmapheresis	Headache, fatigue, and myasthenic ptosis and double vision
Erkmen (2010)	61/F	Seizure, memory deficit	III	Bilateral nonenhancing hyperintense lesions	Yes	VGKC, cell surface antigen (CSF)	Thymectomy, radiation, corticosteroids, IgG	No residual symptoms and disease free

MRI, Magnetic resonance imaging; ANA, antinuclear antibody protein-5; IgG, intravenous immunoglobulin G; CSF, cerebrospinal fluid; WBC, white blood cell count; AchR, acetylcholine receptor; CRMP5, collapsin response mediator; ANNA-I, type 1 antineuronal nuclear antibody; VGCC, voltage-gated calcium channel; VGKC, voltage-gated potassium channel; GAD, glutamic acid decarboxylase; NMDAR, N-methyl-D-aspartate receptor; CV2, crossveinless-2; GluR1, 2, glutamate receptors 1, 2 subunits of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA); dsDNA, double stranded DNA. *Suspected staging based on author's description. Thymoma being stage I; thymic carcinoma being at least stage II or B3.

thymoma would suggest a paraneoplastic syndrome. Although routine analysis of cerebrospinal fluid is nonspecific, sampling of serum and cerebrospinal fluid for antineuronal antibodies (found in 75% of patients with TAPE) will aid in establishing a paraneoplastic pathogenesis. There is little value in a brain biopsy inasmuch as it usually reveals nonspecific lymphocyte and plasma cell infiltration. The diagnosis of TAPE depends on the combination of the encephalitis syndrome, MRI findings, and detection of antineuronal autoantibodies in the setting of a thymic neoplasm.

Once the diagnosis of TAPE has been made, immediate intervention is necessary to prevent progressive neurologic decline and death. Immunotherapy with IgG and corticosteroids³ will improve neurologic symptoms resulting from inflammatory response, but complete resection of the thymoma confers the best chance at disease-free survival from oncologic as well as paraneoplastic standpoints. Antibody titers decrease after thymectomy, thus abating ongoing inflammation and cell death.³ If corticosteroids, IgG, and thymectomy fail to improve neurologic symptoms, diminishing antineuronal antibodies with plasmapheresis

may aid in management of these patients. The treatment of TAPE must address the immune response targeting the nervous system and the underlying thymoma.

Thirty-three percent of patients with TAPE died, all as a consequence of the nervous system compromise. The majority of these patients who died had stage I thymomas. Early Masaoka stage thymomas may produce more functional and neurotoxic autoantibodies than their malignant counterparts.⁴ Therefore, outcome is driven more by ongoing neurologic insult than the underlying thymic disease. Only 21% of patients with TAPE achieved symptom-free survival; all of these patients had complete resection of their thymoma.

With TAPE, it is incumbent on the clinician to make the link between thymoma and encephalitis before progressive neurologic symptoms and death ensue. The reported cases

suggest a role of antineuronal autoantibody production in the pathogenesis and, therefore, in the rationale for treatment options. We believe that immunotherapy and complete resection confer the best chance of symptom-free survival.

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Total correction of tetralogy of Fallot associated with rhabdomyoma in the right ventricle

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Primary cardiac tumors are a rare disease, with a low incidence. Rhabdomyoma, a type of benign primary cardiac tumor, is the most common primary cardiac neoplasm in children and occurs almost exclusively in children. We reported a rare case of an infant with tetralogy of Fallot associated with rhabdomyoma in the right ventricle.

CLINICAL SUMMARY

An 8-month-old male infant had cyanosis and a heart murmur at birth. Physical examination revealed cyanosis, a systolic murmur at the second and third intercostal spaces left of the sternum, and a weakened pulmonary second heart sound. Transthoracic echocardiography showed typical anatomic appearance of tetralogy of Fallot and a 2×2 -cm mass in the right ventricular cavity. Multiple-slice com-

puted tomography confirmed the findings from echocardiography and revealed that the mass was likely to attach to the right side of the interventricular septum (Figure 1). An on-pump open cardiac operation was performed. Cardiopulmonary bypass was established by cannulation of the aorta and venae cavae, and systemic temperature was kept around 28°C for the intracardiac procedure. Cold blood cardioplegia was used to induce and maintain cardiac arrest. A longitudinal incision was made crossing the pulmonary valve annulus, and the $2 \times 2 \times 1$ -cm mass was found attached to the right side of interventricular septum close to cardiac apex, surrounded by muscular trabeculae (Figure 2, A). The base of the mass was about 1.5×1 -cm wide. This mass had a color similar to normal myocardium with a smooth surface and irregular shape (Figure 2, B). The cardiac mass was resected completely, with care taken to cause as little injury to the normal myocardium as possible, followed by correction of tetralogy of Fallot, including infundibulectomy, repair of ventricular septal defect, and transannular pericardial patch (Figure 2, C). This infant was successfully weaned from cardiopulmonary bypass. The mass was investigated pathologically. The immunohistochemical assays showed that stainings of actin (Figure 2, D), desmin, and vimentin were strongly positive. However, staining of S-100 was negative. These histologic findings proved that this cardiac mass was a rhabdomyoma. During

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