Signs heralding appearance of thymomas after extended thymectomy for myasthenia gravis

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Abstract

Purpose of review

Thymomas appear very rarely after extended thymectomy for early-onset myasthenia gravis (EOMG). We describe 2 such cases that highlight potential early warning signs.

Recent findings

In their 20s, one woman and one man developed EOMG (AChR antibody-positive), requiring extended transsternal removal of hyperplastic thymi at ages 35 and 27, respectively. Their myasthenia gravis was readily controlled for the next 10 and 7 years before deteriorating in both, with appearance of late clinical features and anticytokine autoantibodies suggesting underlying thymomas, namely respiratory infections, genital herpes, chronic candidiasis, and alopecia in the woman and erythroderma and lichen planus in the man, followed by *Pseudomonas*, *Klebsiella*, and cytomegalovirus infections plus chronic hepatitis during intensifying immunosuppressive therapy. Type B thymomas were then detected. Despite surgery or radiotherapy, and intensive drug therapy, the patients died 7 and 1 years later.

Summary

Certain infections/dermatologic manifestations that associate with long-standing thymomas may herald their late appearance, despite previous thymectomy.

Thymomas are rare thymic epithelial tumors that are often associated with autoimmune disorders, among which myasthenia gravis (MG) is the commonest.^{1,2} In addition, autoimmune and other mechanisms underlie thymoma-associated humoral and cellular immune defects (e.g., hypogammaglobulinemia) that can lead to life-threatening infections.

Thymectomy is an accepted therapeutic option for early-onset MG (EOMG).³⁻⁵ Extended thymectomy aims to dissect the macroscopically recognizable thymus together with the anterior mediastinal fat, which may harbor substantial thymic extensions on microscopic examination. There are several reports of recurrences of MG because of incomplete removal or ectopy of thymic tissue, but very few of thymomas arising from remnant or ectopic thymic tissue following transsternal thymectomy.⁶⁻¹⁰ Associated diseases, particularly MG, are often

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the presenting manifestation of thymomas, but other features may appear after thymectomy and may sometimes herald thymoma recurrence. This also applies to thymoma-associated immunodeficiencies and subsequent severe or chronic infections such as chronic mucocutaneous candidiasis (CMC), cryptococcal meningitis, and Kaposi sarcoma.²

Some of these features echo the characteristics of the autoimmune polyendocrinopathy, candidiasis, and ectodermal dystrophy (APECED) syndrome. It results from mutations of *AIRE* (autoimmune regulator), which is a crucial gene in the induction of thymic self-tolerance.¹¹ The *AIRE* protein mediates expression of thousands of peripheral tissue-specific self-antigens by medullary thymic epithelial cells; in *AIRE* deficiency states, the autoimmune features are widely attributed to faulty thymic negative selection of autoreactive T cells.¹¹⁻¹³ Interestingly, most MG-associated thymomas not only generate large numbers of T cells but do so in the absence of *AIRE* in ≥90% of these neoplasms¹³⁻¹⁵—possibly explaining why occasional patients, with or without MG, thymectomy some clinical features or autoantibodies typical of APECED (e.g., against type I interferons).¹³⁻¹⁵ In particular, in both syndromes, the CMC apparently uniquely has an autoimmune basis, with autoantibodies neutralizing interleukin (IL)–17A, IL-17F, or IL-22, and loss of TH17 cells.¹¹⁻¹³

We report 2 patients with EOMG and thymic hyperplasia, who underwent extended transsternal thymectomy, and later in life developed clinical manifestations heralding a thymoma.

Case 1

A 20-year-old woman started to experience occasional unilateral eyelid ptosis. A few years later, after child delivery, she developed diplopia, unilateral eyelid ptosis, and mild dysphagia. MG was diagnosed: EMG confirmed decrement of compound muscle action potential (CMAP) amplitude on repetitive stimulation and positive AChR antibodies. Her MG improved with pyridostigmine, but mild ptosis persisted. In 1987, at 35 years of age, her MG worsened, now with limb weakness, mild dysphagia, and dysphonia. It was decided to start treatment with steroids. After this, her MG rapidly worsened, needing intensive care because of respiratory failure. She underwent extended transsternal thymectomy and histology revealed thymic follicular hyperplasia (figure, A).

The patient improved and remained stable (Myasthenia Gravis Foundation of America IIA) for more than 10 years, although steroids could never be completely discontinued.

In 1997, at age 45, the patient developed recurrent respiratory tract infections, some with admission to the intensive care unit for ventilatory support, and worsening myasthenia requiring plasma exchange. Anti-AChR antibodies and CT scan were not checked at this time. She soon presented with chronic oral and genital candidiasis; severe onychomycosis;

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recurrent *Herpes simplex* genital ulcers that were painful and difficult to treat, and became chronic; and alopecia totalis. Because of that and the recurrent severe infections, thymoma was suspected. Thorax MRI confirmed the presence of a mediastinal mass, which was removed via a transsternal approach. Histologic analysis revealed a WHO type B2 thymoma (figure, B). After surgery, she was free of myasthenic symptoms and required no treatment, but she soon developed neck weakness requiring treatment with pyridostigmine and a moderate dose of steroids. Antibodies to AChR were positive at 8.0 nmol/L.

Seven years later, the myasthenic symptoms got worse and were largely refractory to plasma exchange and IV immunoglobulin (IVIg). The patient developed severe recurrent respiratory tract infections, requiring repeated admissions to the intensive care unit. Genital *Herpes simplex* ulcers and onychomycosis also persisted, despite treatment. She died of severe pneumonia at 52 years of age.

Retrospective serology showed high levels of neutralizing antibodies to the proinflammatory interleukins interferon (IFN)– α , IFN– ω , IL-17A, IL-17F, and IL-22 by the time the thymoma was diagnosed. On immunohistochemistry of archival paraffin material, we did not detect any *AIRE*-positive cells in the thymoma, but found some in the hyperplastic thymus removed 17 years previously (figure, C,d), where they might have been depleted by the prior corticosteroid treatment.

Case 2

In June 2003, a 27-year-old man developed generalized weakness, with falls and difficulties in playing football and in chewing, dysphonia, diplopia, and unilateral ptosis. EMG showed CMAP decrement on repetitive nerve stimulation of the facial and cubital nerves and a high titer of AChR antibodies. Generalized MG was diagnosed and he started pyridostigmine, 300 mg/d, with partial improvement. Thorax CT scan showed thymic enlargement. In August 2003, he sustained trauma to his thorax after a fall. His neck and limb weakness worsened and he became dysphagic. He was treated with prednisolone 90 mg/d and pyridostigmine 420 mg/d 20 days later. One month later, he was readmitted for

(A.a–A.d) Thymus was resected in 1987, following 2 months' corticosteroid treatment. Hematoxylin & eosin (H&E). (A.a) Non-neoplastic thymic tissue with attenuated dark-staining cortical areas (moderate involution of the cortex) (H&E $\times 50$). (A.b) Thymus of 1987. Cytokeratin 19 staining highlights epithelial cells in the cortex (C) and medullary epithelial bands (MEB), and lymphoid follicular hyperplasia as revealed by a germinal center (GC) in the keratin-negative infiltrate, which includes (A.c) CD20. Numerous CD20-positive B cells (M). (A.d) AIRE. Staining for AIRE revealed AIRE-positive cells (arrows) in the medulla; their rarity is likely due to corticosteroid treatment. HC = Hassall corpuscle. Immunoperoxidase in b–d, $\times 50$ in b and c, $\times 200$ in d. (B.a–B.d) Overviews of the resection specimen of 1997. (B.a) Thymoma is on the left (black arrowheads). Its capsule separates it from a small non-neoplastic thymic remnant (white arrowheads; H and E $\times 50$), which shows major cortical involution and few HC but a typical keratin-negative infiltrate (B.b CK19) with numerous CD20-positive B cells and MEB. The thymoma stains strongly for epithelial cells (B.b) but not for B cells (B.c CD20). We found no AIRE-positive cells in the thymic remnant (B.d AIRE) again after 2 months' immunosuppressive treatment with corticosteroids. Immunoperoxidase in B.b–B.d, $\times 25$ in B.b and B.c, $\times 100$ in B.d. (C.a–C.d) (C.a) WHO type B2 thymoma with numerous lymphocytes enmeshed by cytokeratin 19–positive epithelial cells (C.b CK19). CD20-positive B cells were rare (C.c CD20), and no AIRE-positive cells were seen (C.d AIRE–), as is typical of $>95\%$ of thymomas, especially of type B2, irrespective of the presence or absence of mucocutaneous candidiasis.^{12,14} Perivascular spaces with extraparenchymal lymphocytes are highlighted by arrows. H&E in C.a, immunoperoxidase in C.b–C.d, $\times 50$ in C.c, $\times 200$ in C.a, C.b, and C.d.

extended transsternal thymectomy. Histology showed thymic follicular hyperplasia (figure, B). Six days after surgery, he developed severe dysphagia and *Herpes zoster* infection at the level of the T8 dermatome. He was successfully treated with IVIg and acyclovir. Five days later, his dysphagia and neck muscle weakness worsened again, and he was plasma exchanged. He soon developed respiratory weakness, requiring mechanical ventilation. At that time, *Staphylococcus aureus* sepsis related to the plasma exchange catheter was diagnosed. Because of the bulbar symptoms, IVIg was repeated and cyclosporine A was started, progressing up to 4 mg/kg/d.

During 2004, the steroids were tapered slowly, and the patient remained stable on cyclosporine 200 mg/d and pyridostigmine 420 mg/d until July 2010. He then developed an erythematous rash spreading from the thorax to the upper limbs, and simultaneously his ocular weakness, dysphonia, and dysphagia reappeared. Steroids were reintroduced but without clear improvement. After 2 skin biopsies, pityriasis rosea and lichen planus were diagnosed. In November 2010, he was readmitted because of bulbar symptoms, proximal tetraparesis, and dyspnea. Thorax CT scan showed a mediastinal mass around the supra-aortic trunk with contrast enhancement and multiple lesions in the pleura. A mediastinal

biopsy showed a thymoma type B3 (figure, B). PET scan suggested that it was invading locally. The skin lesions were later considered to be paraneoplastic erythroderma. He was treated with plasma exchange, but soon declined, again needing mechanical ventilation. Plasma exchange was repeated for 23 sessions. He continued to deteriorate, still dependent on mechanical ventilation and a feeding tube. The tumor was considered unresectable.

The patient had several infections with *Pseudomonas aeruginosa* pneumonia, *Klebsiella* spp. persisting in the respiratory secretions, systemic cytomegalovirus (CMV), chronic hepatitis (hepatitis B virus [HBV] DNA positive) of uncertain cause (CMV, HBV, toxic, or autoimmune), and persistent diarrhea of undetermined cause, with malabsorption, causing severe nutritional deficits. He had a severe immunodeficiency (CD4+ 99/ μ L). Since the patient's condition precluded chemotherapy, radiotherapy (dose 30 Gy) to the mediastinum was performed. His nutritional state slowly improved. In February 2011, he started chemotherapy with cyclophosphamide, doxorubicin, and cisplatin, but, after the first session, his condition deteriorated, again requiring mechanical ventilation. Thoracic CT scan showed a massive pulmonary thromboembolism. Despite treatment with IV heparin, he died 48 hours later.

Retrospective serology from 2010, when the patient's thymoma was diagnosed, revealed high levels of autoantibodies neutralizing IFN- α , IFN- ω , IL-17A, IL-17F, and IL-22.

Discussion

We report 2 patients with early-onset AChR MG, which became more severe and was complicated by more unusual paraneoplastic phenomena concomitantly with detection of thymomas 7–10 years after extended transsternal thymectomy. To our knowledge, only 5 thymomas developing after thymectomy for nonthymomatous MG have been described so far,^{6–10} though with no record of anticytokine autoantibodies, which co-occurred with some clinical features typical of APECED in our patient 1.

Our review of sections from the original thymectomy specimens confirmed the diagnosis of follicular hyperplasia, and provided no evidence that thymomas had been overlooked. Therefore, it is most likely that they arose from thymic remnants that escaped removal during the first surgery in spite of extended transsternal thymectomy. This approach aims to remove all extensions and heterotopic foci of thymic tissue in the mediastinal and part of the cervical fat in addition to the main body of the thymus. However, about 5% of thymic tissue is left behind, by contrast with the obsolete maximal thymectomy approach, which requires combined transsternal and transcervical surgery without apparently improving the control of MG symptoms.¹⁶ Microscopic extensions of thymic tissue may escape surgical removal, especially around and between large vessels in the vicinity of the aortic arch.¹⁷ This possibility is particularly obvious in our patient 2, whose thymoma occurred in an unusual location, around the supra-aortic trunk (see above). The alternative scenario that a late metastasis of an overlooked thymoma was the source of the tumors appears less probable. However, a caveat concerns the paucity of slides that were available for our review of the historic thymectomy material, reflecting the lack of guidelines about how many paraffin blocks should be prepared from non-neoplastic thymectomy specimens. Microthymomas, in particular, may escape macroscopic detection and limited sampling.^{18,19} In fact, on the extensive sampling required in the recent MGTX study on nonthymomatous AChR MG, one unexpected thymoma was detected among 60 thymectomy specimens.⁵ In any case, the admittedly low risk of malignant transformation of remnant thymic tissue should be considered in the debate on whether extensive or limited approaches are preferable in conventional or robotic thymectomy for nonthymomatous MG.^{3,5,16,17,20,21}

An unusual finding is the late onset of immunologic features in addition to MG exacerbations concomitantly with detection of thymomas in both our patients: they also showed identical profiles of neutralizing anticytokine autoantibodies, whether typical of thymoma patients in general (IFN- α , IFN- ω), or of the few with CMC, neutralizing IL-17A, IL-17F, or IL-22, antibodies found in 50%–90% of *AIRE*-mutant

These cases enable us to study the clinical, serologic, and thymic features of MG in both autoimmune and paraneoplastic forms in the same patient.

APECED patients.^{11,12} By contrast, almost all thymomas have shown deficient *AIRE* protein expression in their neoplastic thymic epithelial cells—as in patient 1—despite a wild-type *AIRE* gene.^{13–15} While both APECED features and autoantibodies to TH-17 cytokines do occur in thymoma patients (again like our patient 1), it seems puzzling that they do so only rarely.^{11–15} The parallel rarity of CMC is less surprising, as it correlates with deficiencies in TH17 cells/autoantibodies against their cytokine products.¹¹ It must be relevant that the *AIRE* deficiency in APECED is genomic, and present from conception, whereas, in thymoma patients, it is restricted to their tumors, which arise in adulthood. It is theoretically possible that the prior steroid treatment might have influenced the *AIRE* expression in our patients' thymi or thymomas, whether via direct effects on medullary epithelial cells or indirectly via depletion of interacting thymocytes, or via other actions. We are not aware of literature that firmly supports any such possibility in humans. There is one report of reduction in *AIRE* expression in Epstein-Barr virus–transformed human B-cell lines treated with dexamethasone in vitro,²² but its applicability to medullary epithelial cells in vivo is questionable.

While some thymoma patients (~5%) have bone marrow aplasias or hypogammaglobulinemia, a few others apparently with longstanding or inoperable thymomas¹³ have deficiencies in CD4+ T cells or B cells,^{22–25} or various infections or skin conditions,^{11–13,23–26} as in our patient 2. These latter features may correlate better with the autoantibodies against IL-12 and Th17 cytokines than against type I Interferons, but it is difficult to be sure of any contribution, as they occur mainly in patients with long and complicated histories, including treatments with varied immunosuppressants.²⁷

Conclusion

These cases enable us to study the clinical, serologic, and thymic features of MG in both autoimmune and paraneoplastic forms in the same patient. It is also most remarkable that they both developed unusual APECED-type manifestations and autoantibodies—or immunodeficiency—in the context of thymomas arising within 10 years of removal of hyperplastic thymi. Not only are the alopecia and severe recurrent infections, particularly the mucocutaneous candidiasis, known complications of thymoma: they are also signs

TAKE-HOME POINTS

- Thymomas appear very rarely after extended thymectomy for early-onset myasthenia gravis.
- Certain infections/dermatologic manifestations that associate with long-standing thymomas may invaluablely herald their late appearance, despite previous thymectomy.
- Thymoma-associated anticytokine autoantibodies may invaluablely herald thymomas' late appearance.

of complex underlying immunodeficiencies, some of which have an autoimmune basis, as in APECED. If our patients had not developed those unusual additional manifestations, their tumors might have gone undetected; these seem too rare in longstanding EOMG patients to justify routine 5-yearly screening for titin or striated muscle antibodies. However, a thymoma should be considered in any patient who develops such complications, or whose MG becomes refractory to treatments, without other obvious explanations.

Author contributions

E. Santos: drafting/revising the manuscript, data acquisition, study concept or design, analysis or interpretation of data. A.M. Silva: drafting/revising the manuscript, data acquisition. P. Stroebel: drafting/revising the manuscript, analysis or interpretation of data. A. Marinho: drafting/revising the manuscript, data acquisition. N. Willcox: drafting/revising the manuscript, analysis or interpretation of data. G. Goncalves: analysis or interpretation of data. C. Lopes: study concept or design, analysis or interpretation of data, study supervision. A. Marx: drafting/revising the manuscript, data acquisition, analysis or interpretation of data, pathologic evaluation. M.I. Leite: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, study supervision.

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References

1. Tomaszek S, Wigle DA, Keshavjee S, Fischer S. Thymomas: review of current clinical practice. *Ann Thorac Surg* 2009;87:1973–1980.
2. Schmidt S, Padberg F. Late onset immunodeficiency in a patient with recurrent thymic carcinoma and myasthenia gravis. *J Neurol Sci* 1998;157:201–205.
3. Masaoka A, Nagaoka Y, Kotake Y. Distribution of thymic tissue at the anterior mediastinum: current procedures in thymectomy. *J Thorac Cardiovasc Surg* 1975;70:747–754.
4. Olanow CW, Wechsler AS, Sirotkin-Roses M, Stajich J, Roses AD. Thymectomy as primary therapy in myasthenia gravis. *Ann NY Acad Sci* 1987;505:595–606.
5. Wolfe GI, Kaminski HJ, Sonnett JR, Aban IB, Kuo HC, Cutter GR. Randomized trial of thymectomy in myasthenia gravis. *N Engl J Med* 2016;375:511–522.
6. Katzberg HD, Miller RG, Katz J. Thymic carcinoma in myasthenia gravis developing years after thymectomy. *Muscle Nerve* 2009;40:137–138.
7. Hirabayashi H, Ohta M, Okumura M, Matsuda H. Appearance of thymoma 15 years after extended thymectomy for myasthenia gravis without thymoma. *Eur J Cardiothorac Surg* 2002;22:479–481.
8. Toker A, Tanju S, Ozluk Y, Serdaroglu P. Thymoma appearing 10 years after an extended thymectomy for myasthenia gravis. *Eur J Cardiothorac Surg* 2008;33:1155–1156.
9. Vasiliki Z, Georgios V, Dimitra R, Charalambos Z. Appearance of thymoma 5 Years after thymectomy for nonthymomatous myasthenia gravis. *J Clin Neuromuscul Dis* 2014;16:42–43.
10. Husain F, Ryan NJ, Hogan GR, Gonzalez E. Occurrence of invasive thymoma after thymectomy for myasthenia gravis: report of a case. *Neurology* 1990;40:170–171.
11. Kisand K, Lilic D, Casanova J-LL, Peterson PP, Meager A, Willcox N. Mucocutaneous candidiasis and autoimmunity against cytokines in APECED and thymoma patients: clinical and pathogenetic implications. *Eur J Immunol* 2011;41:1517–1527.
12. Kisand K, Boe Wolff AS, Podkrajsek KT, et al. Chronic mucocutaneous candidiasis in APECED or thymoma patients correlates with autoimmunity to Th17-associated cytokines. *J Exp Med* 2010;207:299–308.
13. Wolff AS, Kämer J, Owe JF, et al. Clinical and serologic parallels to APS-1 in patients with thymomas and autoantigen transcripts in their tumors. *J Immunol* 2014;193:3880–3890.
14. Ströbel P, Murumägi A, Klein R, et al. Deficiency of the autoimmune regulator AIRE in thymomas is insufficient to elicit autoimmune polyendocrinopathy syndrome type 1 (APS-1). *J Pathol* 2007;211:563–571.
15. Cheng MH, Fan U, Grewal N, et al. Acquired autoimmune polyglandular syndrome, thymoma, and an AIRE defect. *N Engl J Med* 2010;362:764–766.
16. Masaoka A. Extended trans-sternal thymectomy for myasthenia gravis. *Chest Surg Clin N Am* 2001;11:369–387.
17. Jaretzki A, Bethea M, Wolff M, et al. A rational approach to total thymectomy in the treatment of myasthenia gravis. *Ann Thorac Surg* 1977;24:120–130.
18. Cheuk W, Tsang WY, Chan JK. Microthymoma: definition of the entity and distinction from nodular hyperplasia of the thymic epithelium (so-called microscopic thymoma). *Am J Surg Pathol* 2005;29:415–419.
19. Fukuhara M, Higuchi M, Owada Y, et al. Clinical and pathological aspects of microscopic thymoma with myasthenia gravis and review of published reports. *J Thorac Dis* 2017;9:1592–1597.
20. Lo CM, Lu HI, Hsieh MJ, Lee SS, Chang JP. Thymectomy for myasthenia gravis: video-assisted versus transsternal. *J Formos Med Assoc* 2014;113:722–726.
21. Brenna G, Antozzi C, Montomoli C, Baggi F, Mantegazza R; INCB-MG Group. A propensity score analysis for comparison of T-3b and VATET in myasthenia gravis. *Neurol* 2017;89:189–195.
22. Maranville JC, Luca F, Richards AL, et al. Interactions between glucocorticoid treatment and cis-regulatory polymorphisms contribute to cellular response phenotypes. *PLoS Genet* 2011;7:e1002162.
23. Holbro A, Jauch A, Lardinois D, Tzankov A, Dirnhofer S, Hess C. High prevalence of infections and autoimmunity in patients with thymoma. *Hum Immunol* 2012;73:287–290.
24. Masci AM, Palmieri G, Vitiello L, et al. Clonal expansion of CD8+ BV8 T lymphocytes in bone marrow characterizes thymoma-associated B lymphopenia. *Blood* 2003;101:3106–3108.
25. Yel L, Liao O, Lin F, Gupta S. Severe T- and B-cell immune deficiency associated with malignant thymoma. *Ann Allergy Asthma Immunol* 2003;91:501–505.
26. Tarr PE, Sneller MC, Mechanic LJ, et al. Infections in patients with immunodeficiency with thymoma (good syndrome): report 5 cases and review of the literature. *Medicine* 2001;80:123–133.
27. Willcox N, Leite MI, Kadota Y, et al. Autoimmunizing mechanisms in thymoma and thymus. *Ann NY Acad Sci* 2008;1132:163–173.