Mod Rheumatol (2007) 17:63–66
DOI 10.1007/s10165-006-0535-x

CASE REPORT

**Yoshito Yoshidome · Shigeaki Hayashi
Yoshikazu Maruyama · Toshi Yoneda
Daisuke Matsuzoe · Takehito Kawakami
Hiroshi Shirahama · Yukie Tashiro · Nobutaka Eiraku**

A case of mixed connective tissue disease complicated with thymic carcinoma and Hashimoto's thyroiditis

Received: July 31, 2006 / Accepted: September 27, 2006

Abstract We report the case of a 63-year-old woman who suffered from mixed connective tissue disease (MCTD) complicated with thymic carcinoma and Hashimoto's thyroiditis. Although many systemic syndromes associated with thymoma and thymic carcinoma, i.e., myasthenia gravis, pure red cell aplasia, hypogammaglobulinemia, and Hashimoto's thyroiditis, are known, this is the first report of MCTD complicated with thymic carcinoma. It was suggested that MCTD may be a paraneoplastic syndrome associated with thymic carcinoma.

Key words Hashimoto's thyroiditis · Mixed connective tissue disease · Paraneoplastic syndrome · Thymic carcinoma

Introduction

Mixed connective tissue disease (MCTD) is defined as a generalized connective tissue disorder characterized by the presence of high titer anti-U1 ribonucleoprotein (RNP) antibodies in combination with clinical features commonly seen in systemic lupus erythematosus (SLE), systemic sclerosis (SSc), and polymyositis (PM).[1] Thymomas and thymic carcinomas are associated with a variety of paraneoplastic disorders, many of which are autoimmune or endocrine in nature.[2] The most clinically important of these are myasthenia gravis (MG), pure red cell aplasia, hypogammaglobulinemia, and collagen vascular diseases.[3] In this case report, we present a patient with MCTD complicated with thymic carcinoma and Hashimoto's thyroiditis. This is the first report of MCTD complicated with thymic carcinoma.

Y. Yoshidome[1] (✉) · S. Hayashi · Y. Maruyama
Department of Neurology, Imakiire General Hospital, Kagoshima, Japan

T. Yoneda · D. Matsuzoe · T. Kawakami
Department of Chest Surgery, Imakiire General Hospital, Kagoshima, Japan

H. Shirahama · Y. Tashiro
Department of Pathology, Imakiire General Hospital, Kagoshima, Japan

N. Eiraku
Health Service Center, Kagoshima University, Kagoshima, Japan

Correspondence address:
[1]Department of Neurology and Geriatrics, Kagoshima University Graduate School of Medical and Dental Sciences, 8-35-1 Sakuragaoka, Kagoshima 890-8520, Japan
Tel. +81-99-275-5332; Fax +81-99-265-7164
e-mail: yoshidomey@mub.biglobe.ne.jp

Case report

A 63-year-old Japanese woman was admitted to our hospital on May 31, 2002, because of a 5-month history of numbness in her right arm and Raynaud's phenomenon. She had been treated for hypertension with imidapril for 15 years. There was no relevant family history. On admission, her height was 151.0 cm, her weight was 62.0 kg, and her body mass index was 27.2. Her body temperature was 37.3ºC, pulse rate 78 beats/min, blood pressure 146/80 mmHg, and respiration rate 18/min. Her thyroid was not enlarged. There were no abnormal findings in the chest or abdomen. Swollen fingers and Raynaud's phenomenon both were apparent. Neurological examination found no abnormalities suggestive of MG, including no ptosis, no muscle weakness, no dysarthria, no dysphagia, and no dyspnea. Laboratory studies showed the following values: white blood cell count, 3980/mm^3; hemoglobin, 13.6 g/dl; platelets, 22.3 × 10^4/mm^3. The results of biochemistry were as follows: aspartate aminotransferase level, 18 IU/l; alanine aminotransferase level, 17 IU/l; lactate dehydrogenase level, 362 IU/l; cholinesterase level, 238 IU/l; conjugated bilirubin level, 0.3 mg/dl; unconjugated bilirubin level, 0.7 mg/dl; alkaline phosphatase level, 362 IU/l; gamma-glutamyl transpeptidase level, 37 IU/l; blood urea nitrogen level, 20.3 mg/dl; creatinine level, 1.0 mg/dl; creatine kinase, 51 IU/l; sodium, 143 mEq/l; potassium, 4.0 mEq/l; chloride, 106 mEq/l. Total serum protein level was normal at 7.1 g/dl and electrophoresis showed no hypogammaglobulinemia (18.3%). C-reactive protein level was 0.32 mg/dl and erythrocyte sedimentation rate was

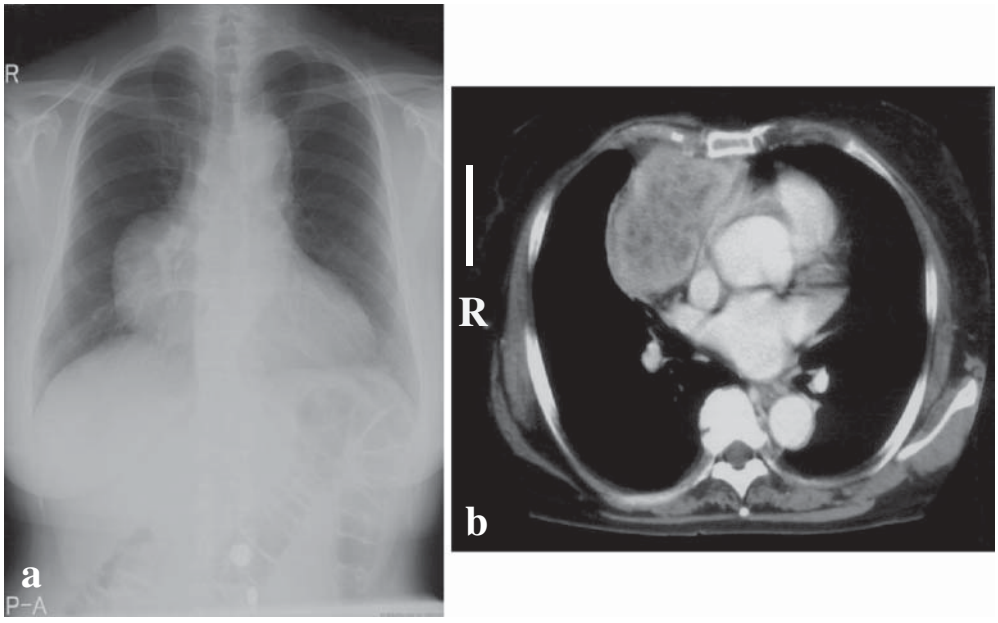

Fig. 1. Chest X-ray (**a**) and chest contrast-enhanced computed tomography (**b**) on admission showed a 10-cm-sized right anterior mediastinal mass infiltrating along the pericardium and pleura with some necrosis, which suggested thymic carcinoma. *Bar* 5 cm

79 mm/h. Urinalysis showed normal findings. Antinuclear antibody was positive at a titer of 1:1280 with a speckled pattern. Anti-U1-RNP antibody was 319.9 U/ml (normal <7.0) and anti-SS-A /Ro antibody was 131.2 U/ml (normal <7.0). Anti-Sm antibody, anti-dsDNA antibody, lupus anticoagulant, anti-β2-glycoprotein antibody, anti-Scl70 antibody, anti-Jo1 antibody, rheumatoid factor, anti-SS-B/La antibody, and antiacetylcholine receptor antibody (AChR-Ab) were absent. CH_{50}, C3, and C4 complements were all normal. Thyroid hormone tests revealed free T3 at 1.96 pg/ml (normal 2.0–5.0), free T4 at 0.72 ng/dl (normal 0.8–1.6), and thyroid-stimulating hormone (TSH) at 4.51 μIU/ml (normal 0.4–4.0). Antithyroid peroxidase antibody (anti-TPO Ab) was positive. Human T-cell lymphotropic virus type I (HTLV-I) serology was positive. Doppler echocardiography was performed. She had no symptoms directly attributable to pulmonary hypertension, including no dyspnea on exertion, no fatigue, no chest pain, and no edema. However, the maximum tricuspid regurgitant jet velocity was recorded and the pulmonary artery pressure (PAP) was calculated on 44 mmHg (normal <40) by the modified Bernoulli equation. A chest X-ray and a chest contrast-enhanced computed tomography showed a 10-cm-sized right anterior mediastinal mass infiltrating along the pericardium and pleura with some necrosis, which suggested thymic carcinoma (Fig. 1a,b). Other radiographic surveys including an abdomen contrast-enhanced computed tomography, a brain magnetic resonance imaging, and a bone scintigram revealed no metastasis. Electromyography (EMG) revealed no decremental response.

A diagnosis of MCTD was made on the basis of swollen fingers, Raynaud's phenomenon, positive anti-U1-RNP antibody, leukopenia, and pulmonary hypertension. We also gave a diagnosis of Hashimoto's thyroiditis based on primary hypothyroidism and positive anti-TPO Ab. On June 27 (day 28), extended thymo-thymomectomy was performed. The tumor was a 10-cm-sized mass infiltrating along the pericardium with some necrosis, which was Masaoka's stage III (Fig. 2). Therefore the patient also underwent the partial resection of pericardium invaded by the tumor. Histologically, the tumor was mainly poorly differentiated squamous cell carcinoma consisting of cytologically malignant tumor cells (Fig. 3a,b), which had CD5 positivity (Fig. 3c). On this basis we made a diagnosis of thymic carcinoma. As postoperative irradiation, 50 Gy were administered to the tumor bed and adjacent mediastinum. Treatment began with prednisolone at 40 mg/day for pulmonary hypertension. Hashimoto's thyroiditis was effectively treated with levothyroxine sodium at 50 μg/day. The numbness in her right arm disappeared as soon as the operation was performed, which was considered to be related with thymic carcinoma. Raynaud's phenomenon treated with nifedipine showed no improvement. Although the doses of predniso-

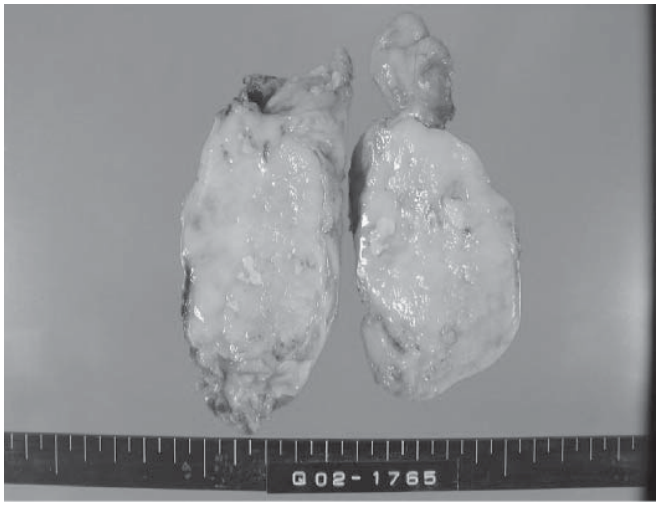

Fig. 2. Macroscopic aspect of the thymic carcinoma. The tumor was a 10-cm-sized mass infiltrating along pericardium with some necrosis

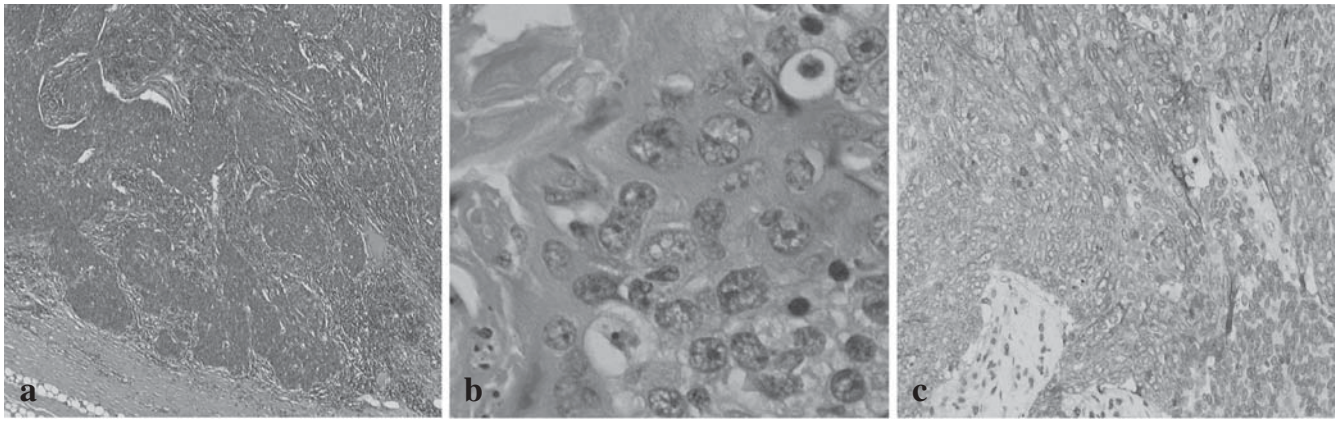

Fig. 3. **a** Histological findings of the tumor showing mainly poorly differentiated squamous cell carcinoma consisted of cytologically malignant tumor cells (H&E stain, ×10). **b** A high-power field of **a** (H&E stain, ×100). **c** The tumor cells had CD5 positivity (CD5 stain, ×40)

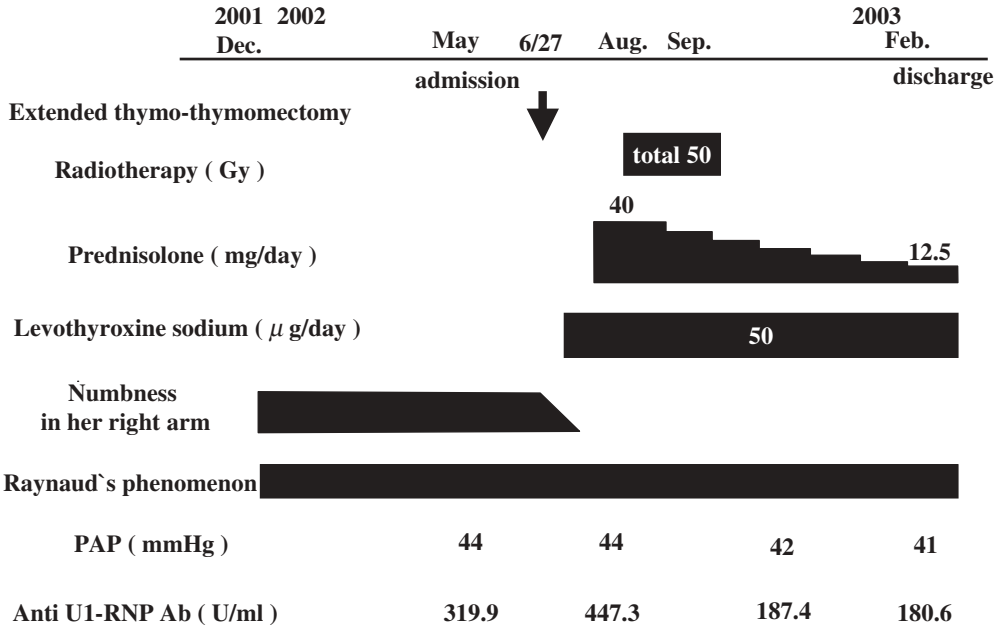

Fig. 4. The clinical course of this case. *PAP*, pulmonary artery pressure estimated by Doppler echocardiography; *U1-RNP Ab*, U1 ribonucleoprotein antibody

lone were gradually tapered and were then maintained at 12.5 mg/day, Doppler echocardiography provided no evidence for an exacerbation of pulmonary hypertension and the titer of anti-U1-RNP antibody also decreased. The patient was discharged without recurrence of thymic carcinoma on February 19, 2003 (day 265). Figure 4 summarizes the patient's clinical course. She has had no recurrence of thymic carcinoma and no exacerbation of pulmonary hypertension up to now.

Discussion

This patient presented with manifestations of MCTD, Hashimoto's thyroiditis, and thymic carcinoma. We gave a diagnosis of MCTD based on swollen fingers, Raynaud's phenomenon, positive anti-U1-RNP antibody, SLE-like finding, i.e., leukopenia, and pulmonary hypertension, although she had non-SSc-like and non-PM-like findings.[4] Hashimoto's thyroiditis was also diagnosed on the basis of primary hypothyroidism and positive anti-TPO Ab.[5,6] Histological appearances of the surgical resected anterior mediastinal huge tumor were mainly poorly differentiated squamous cell carcinoma consisting of cytologically malignant tumor cells, which had CD5 positivity.[7,8] This confirmed the diagnosis of thymic carcinoma. She had no abnormal findings suggesting MG, i.e., no ptosis, no muscle weakness, no dysarthria, no dysphagia, no dyspnea, no decremental response EMG, and no positive AChR-Ab.

There are limited data on the frequency of thyroid disease in MCTD. One report of 22 patients with MCTD found antithyroid antibodies in 23% and hypothyroidism in 16%.[9] A wide variety of paraneoplastic disorders are associated with thymomas and thymic carcinomas.[2] The most clinically important of these are MG, pure red cell aplasia,

and hypogammaglobulinemia.[3] Myasthenia gravis is associated with thymoma in 30–50% of cases.[3] Other paraneoplastic syndromes are found in association with thymoma in 10% of cases;[3] more than one disorder may be present. The symptoms of these associated disorders often lead to the original discovery of the mediastinal tumor.[2] Autoimmune diseases (SLE,[10] PM,[11] SSc,[12] myocarditis,[13] Sjögren's syndrome,[14] ulcerative colitis,[15] Hashimoto's thyroiditis,[16] rheumatoid arthritis,[17] and sarcoidosis[18]) and endocrine disorders (hyperthyroidism,[19] hyperparathyroidism,[20] Addison's disease,[21] and panhypopituitarism[21]) are also common as paraneoplastic syndromes associated with thymoma and thymic carcinoma. Blood disorders, such as T-cell deficiency syndrome,[22] pernicious anemia,[22] erythrocytosis,[23] T-cell lymphocytosis,[11] pancytopenia,[16] and megakaryocytopenia[24] have been noted. Other than MG, neuromuscular syndromes include myotonic dystrophy[25] and Eaton–Lambert syndrome.[26] Miscellaneous disease include hypertrophic osteoarthropathy,[27] nephrotic syndrome,[28] minimal change nephropathy,[29] pemphigus,[30] and chronic mucocutaneous candidiasis.[31]

Primary thymic carcinoma is a rare neoplasm. At the National Cancer Center of Tokyo, 17 cases were resected over a 29-year period, during which time 79 thymomas and 2500 lung cancers were treated.[32] Thymic carcinoma is classically not associated with paraneoplastic syndromes as much as thymoma. As far as we know, this is the first report of a case of MCTD complicated with thymic carcinoma.

In conclusion, we have presented a case report of MCTD complicated with thymic carcinoma and Hashimoto's thyroiditis. It is suggested that MCTD may be a paraneoplastic syndrome associated with thymic carcinoma, although it is necessary to accumulate further cases to define the associational characteristics of these diseases.

References

1. Bennett RM. Mixed connective tissue disease and other overlap syndromes. In: Ruddy S, Harris ED Jr, Sledge CB, editors. Kelley's Textbook of Rheumatology. 6th ed. Philadelphia: WB Saunders; 2001. p. 1241–59.
2. Cameron RB, Loehrer PJ, Thomas CR Jr. Neoplasms of the mediastinum. In: DeVita VT Jr, Hellman S, Rosenberg SA, editors. Cancer principles and practice of oncology. 6th ed. Philadelphia: Lippincott Williams and Wilkins; 2001. p. 1019–36.
3. Lewis JE, Wick MR, Scheithauer BW, Bernatz PE, Taylor WF. Thymoma. A clinicopathologic review. Cancer 1987;60:2727–43.
4. Doria A, Ghirardello A, de Zambiasi P, Ruffatti A, Gambari PF. Japanese diagnostic criteria for mixed connective tissue disease in Caucasian patients. J Rheumatol 1992;19:259–64.
5. Mariotti S, Caturegli P, Piccolo P, Barbesino G, Pinchera A. Antithyroid peroxidase autoantibodies in thyroid disease. J Clin Endocrinol Metab 1990;71:661–9.
6. Nordyke RA, Gilbert FI Jr, Miyamoto LA, Fleury KA. The superiority of antimicrosomal over antithyroglobulin antibodies for detecting Hashimoto's thyroiditis. Arch Intern Med 1993;153: 862–5.
7. Berezowski K, Grimes MM, Gal A, Kornstein MJ. CD5 immunoreactivity of epithelial cells in thymic carcinoma and CASTLE using paraffin-embedded tissue. Am J Clin Pathol 1996;106:483–6.
8. Hishima T, Fukayama M, Fujisawa M, Hayashi Y, Arai K, Funata N, et al. CD5 expression in thymic carcinoma. Am J Pathol 1994;145:268–75.
9. Hameenkorpi R, Hakala M, Ruuska P, Makitalo R, Tiilikainen A, Forsberg S. Thyroid disorder in patients with mixed connective tissue disease. J Rheumatol 1993;20:602–3.
10. Boonen A, Rennenberg R, van der Linden S. Thymoma-associated systemic lupus erythematosus, exacerbating after thymectomy. A case report and review of the literature. Rheumatology (Oxford) 2000;39:1044–6.
11. Cranney A, Markman S, Lach B, Karsh J. Polymyositis in a patient with thymoma and T cell lymphocytosis. J Rheumatol 1997;24: 1413–6.
12. Ben-Shahar M, Rosenblatt E, Green J, Cohen I. Malignant thymoma associated with progressive systemic sclerosis. Am J Med Sci 1987;294:262–7.
13. Kilgallen CM, Jackson E, Bankoff M, Salomon RN, Surks HK. A case of giant cell myocarditis and malignant thymoma: a postmortem diagnosis by needle biopsy. Clin Cardiol 1998;21:48–51.
14. Insler MS, Shelin RG. Sjögren's syndrome and thymoma. Am J Ophthalmol 1987;104:90–1.
15. Okubo K, Kondo N, Okamoto T, Isobe J, Ueno Y. Excision of an invasive thymoma: a cure for ulcerative colitis? Ann Thorac Surg 2001;71:2013–5.
16. Dawson MA. Thymoma associated with pancytopenia and Hashimoto's thyroiditis. Am J Med 1972;52:406–10.
17. Tani K, Matsunaga K, Katoh K, Kawai T, Ueda A, Kase M, et al. Thymoma associated with rheumatoid arthritis after D-penicillamine treatment. Br J Rheumatol 1998;37:472–3.
18. Tanaka F, Yoshitani M, Esaki H, Isobe J, Inoue R, Ito M, et al. A malignant thymoma combined with sarcoidosis (in Japanese). Kyobu Geka 1990;43:823–5.
19. Chen HM, Tsai CP, Lin KP, Wang SJ, Wu ZA, Kao KP. Myasthenia gravis complicated with hyperthyroidism, thymoma and serological evidence of systemic lupus erythematosus: a case report. Zhonghua Yi Xue Za Zhi (Taipei) 1996;58:62–5.
20. Suzuki T, Suzuki S, Kitami A, Hori G, Inoue T, Suzuki S, et al. A thymoma associated with hyperparathyroidism. Thorac Cardiovasc Surg 1997;45:211–2.
21. Souadjian JV, Enriquez P, Silverstein MN, Pepin JM. The spectrum of diseases associated with thymoma. Coincidence or syndrome? Arch Intern Med 1974;134:374–9.
22. Soppi E, Eskola J, Roytta M, Veromaa T, Panelius M, Lehtonen A. Thymoma with immunodeficiency (Good's syndrome) associated with myasthenia gravis and benign IgG gammopathy. Arch Intern Med 1985;145:1704–7.
23. Sundstrom C. A case of thymoma in association with erythrocytosis. Acta Pathol Microbiol Scand [A] 1972;80:235–40.
24. Sundstrom C, Lundberg D, Werner I. A case of thymoma in association with megakaryocytopenia. Acta Pathol Microbiol Scand [A] 1972;80:487–90.
25. Kudva GC, Maliekel K, Kim HJ, Naunheim KS, Stolar C, Fletcher JW, et al. Thymoma and myotonic dystrophy: successful treatment with chemotherapy and radiation: case report and review of the literature. Chest 2002;121:2061–3.
26. Ihara Y, Kuroda S, Otsuki S. A case of malignant thymoma associated with Eaton-Lambert-type neuromuscular transmission block and sensorimotor neuropathy (in Japanese). Rinsho Shinkeigaku 1990;30:750–3.
27. Gharbi A, Benjelloun A, Ouzidane L, Ksiyer M. Hypertrophic osteoarthropathy associated with malignant thymoma in a child. J Radiol 1997;78:303–4.
28. Schillinger F, Milcent T, Wolf C, Gulino R, Montagnac R. Nephrotic syndrome as the presenting feature of malignant thymoma. Nephrol Dial Transplant 1997;12:2732–4.
29. Zinger C, Ben-Itzhak O, Szylman P, Green J, Nakhoul F. Minimal-change nephropathy and malignant thymoma. Am J Nephrol 1998;18:61–3.
30. Lynfield YL, Pertschuk LP, Zimmerman A. Pemphigus erythematosus provoked by allergic contact dermatitis. Occurrence many years after thymoma removal. Arch Dermatol 1973;108:690–3.
31. Palestine RF, Su WP, Liesegang TJ. Late-onset chronic mucocutaneous and ocular candidiasis and malignant thymoma. Arch Dermatol 1983;119:580–6.
32. Shimosato Y, Mukai K. Tumors of the thymus and related lesions. In: Shimosato Y, Mukai K, editors. Tumors of the mediastinum. 3rd ed. Washington, DC: Armed Forces Institute of Pathology; 1995. p. 33–247.