Cellular & Molecular Immunology (2011) 8, 199–202

www.nature.com/cmi

REVIEW

Thymoma and autoimmunity

Shahar Shelly[1], Nancy Agmon-Levin[1,2], Arie Altman[1,2] and Yehuda Shoenfeld[1,2,3]

The thymus is a central lymphatic organ that is responsible for many immunological functions, including the production of mature, functional T cells and the induction of self-tolerance. Benign or malignant tumors may originate from the thymus gland, with thymoma being the most common and accounting for 50% of anterior mediastinal tumors. Malignancies linked to thymoma include the loss of self-tolerance and the presence of autoimmunity. In this review, we compiled the current scientific evidence detailing the various interactions between thymoma and autoimmune diseases, including myasthenia gravis, systemic lupus erythematosus, inappropriate antidiuretic hormone secretion, pure red cell aplasia, pernicious anemia, pemphigus and autoimmune thyroid diseases. In recent years, several mechanisms have been proposed to explain these interactions. Most are based on the assumption that the 'sick' thymus, like the 'normal' thymus, can generate mature T cells; however, the T cells generated by the sick thymus are impaired and thus may exert cellular autoreactivity. Here, we present several theories that may shed light on the loss of self-tolerance associated with this epithelial tumor of the thymus.
Cellular & Molecular Immunology (2011) **8,** 199–202; doi:10.1038/cmi.2010.74; published online 14 February 2011

Keywords: autoimmune diseases; autoimmunity; self-tolerance; thymoma; thymus

INTRODUCTION

The word 'thymus' originates from a Latin derivation of the Greek *thymus*, which means 'warty excrescent'; it is so named because it resembles the flowers of the thyme plant. *Thymus* can also be translated as 'soul' or 'spirit', and thus the thymus was misrepresented by Greek physicians as the seat of the soul. The organ was first mentioned by Galen, who noticed that it is located in the anterior mediastinum and is proportionally largest during infancy. However, Galen wrongly assumed that the thymus plays a role in the purification of the nervous system. Later, it was discovered that the thymus is a lymphatic organ, and in 1846 Hassall and Vanarsdale used a novel microscopy technique to study the thymus. They described differences between the thymus and other lymphoid tissues, specifically the characteristic histological feature that became known as Hassall's corpuscles.[1] Additionally, they found that, although the thymus gland undergoes a process of involution, resulting in a reduction in its functioning mass during puberty, it continues to function throughout one's life.

Many immunological functions of the thymus have been elucidated, including development of immunocompetent T cells, differentiation and proliferation of T-cell subsets, such as the evolution of naive T-cells into T helper cells (CD4) and cytotoxic suppressor cells (CD8), and migration of mature T cells into the circulating lymphocyte pool and peripheral tissues.[2] Perhaps the most important role of the thymus, however, is the induction of immune self-tolerance that functions to prevent self-harm or autoimmunity. Additionally, the thymus is capable of secreting hormones and soluble factors, the most notable being thymolin, thymopoietin and thymosin alpha-1. These hormones function in concert to regulate numerous complex interactions controlling the production of mature and functional T cells within the thymus and peripheral tissues.[1]

As with other lymphatic organs, benign or malignant tumors may originate from the thymus. Among these tumors, benign epithelial thymoma is the most common and accounts for 20–25% of all mediastinal tumors and 50% of anterior mediastinal ones.[3] Currently, two means of thymoma classification are used for clinical staging and prognostic evaluations.[4] The first is the WHO classification published in 1999, which utilizes microscopic histological criteria (Table 1), and the second is that performed by Masaoka, which uses macroscopic and microscopic criteria.[3] The current treatment regimen and prognosis for patients diagnosed with thymoma varies according to the stage or subtype of each classification system.[5] In addition, among lymphatic tumors, thymomas are associated with the highest frequency of paraneoplastic manifestations. These include autoimmune phenomena and diseases,[2] which form the basis for this review.

AUTOIMMUNE DISEASES AND THYMOMA

In 1672, Thomas Willis[6] reported the first clinical description of a disease characterized by severe distal muscle weakness. One hundred years later, this disease was termed myasthenia gravis (MG). In 1960, almost 300 years after the initial description of this disease, the presence of autoantibodies to muscle striations in the sera of MG patients was demonstrated, suggesting autoimmunity as the pathogenic mechanism underlying this disease. MG autoantibodies were found to be directed against the acetylcholine receptor

[1]The Zabludovicz Center for Autoimmune Diseases, Sheba Medical Center, Tel-Hashomer, affiliated with Sackler Faculty of Medicine, Tel Aviv University, Israel; [2]Department of Medicine 'B', Sheba Medical Center, Tel-Hashomer, Israel and [3]Sackler Faculty of Medicine, Incumbent of the Laura Schwarz-Kip Chair for Research of Zabludowitz Center for Autoimmune Diseases, Tel-Aviv University, Tel-Aviv, Israel
Correspondence: Dr Y Shoenfeld, Department of Medicine 'B', The Chaim Sheba Medical Center, Tel-Hashomer 52621, Israel.
E-mail: shoenfel@post.tau.ac.il
Received 1 December 2010; accepted 2 December 2010

(AChR) in the neuromuscular junction of skeletal muscles.[7] Normally, when impulses travel down the nerve, the nerve endings release acetylcholine, which binds to AChR, ultimately generating a muscle contraction. Anti-AChR antibodies cause a defect in the transmission of nerve impulses to muscles and diminish muscle contraction by blocking, altering or destroying the receptors for acetylcholine.[8] MG, therefore, is characterized by fatigability of both bulbar and distal muscles, as well as loss of strength upon exertion that improves after rest. The role of humeral immunity in MG is central, but cellular immunity has also been implicated in the close interactions between thymoma and MG. The exact role of the thymus and cellular immunity in the pathogenesis of this autoimmune disease is not clear; however, 75% of patients with MG demonstrate some degree of thymus abnormality, including thymic hyperplasia in 85% of those patients and thymoma in 15% of cases.[6] Additionally, in the study by Okumura *et al.*,[9] a strong connection was documented between MG and thymoma in 467 MG patients who underwent thymectomy between 1962 and 2001. The majority of patients were female, and no sex differences were documented between patients with thymoma-associated MG and those with non-thymoma MG.[9] Furthermore, a link was found between MG and certain types of thymomas (B1 and B2) that matched the WHO classifications (Table 1). These thymomas contain a significant number of $CD4^+/CD8^+$ double-positive T cells, indicating that a malfunction of the thymus medullary selection process observed in these types of thymomas could be the cause of autoreactive T-cell release. Soltys *et al.*[8] also demonstrated a change in the course of the disease following thymus resection. In patients with thymoma-associated MG, a reduction of anti-AChR antibody titer was observed, suggesting a role for the intrathymic germinal centers (characteristic of thymoma) in the pathogenesis of MG. In another study, Okumura *et al.*[9] reported that prethymectomy anti-AChR antibody levels can be viewed as a risk factor for post-thymectomy MG.

In addition to the clinical improvement post-tymectomy and the strong associations between MG and thymoma, it was shown that patients with thymoma-associated MG can be further divided into three subgroups distinguished according to the different clinical manifestations and autoantibodies displayed in their sera. The first group presents with myositis or myocarditis and anti-ryanodine receptor antibodies. The second group displays neuromyotonia and lack of anti-ryanodine receptor antibodies in the presence of voltage-gated or calcium channel autoantibodies. The third group has no myositis, neuromyotonia or anti-ryanodine receptor antibodies, instead presenting with antibodies directed at titin (a large abundant protein also known as connectin) or calcium channel. These differences were hypothesized to be due to the differences in thymoma types and their relation to different autoantibodies, with each being directed against a different component of the muscle tissue.[10] Of note, the association between thymoma and MG was demonstrated over a wide range of ages, including a recent case report of thymoma and MG in infancy.[11]

Besides MG, in which thymoma was the most prevalent, this tumor is also known to be associated with other autoimmune diseases (Table 2), and defective immune regulation has been suggested to be the link between these diseases.[12,13] In 30% of patients with thymoma, autoimmune conditions will be diagnosed either in a comorbid state or at post-thymectomy, where up to 50% of patients are diagnosed concomitantly with two autoimmune diseases.[14,15] The co-occurrence of systemic lupus erythematosus (SLE) and thymoma is estimated to vary between 1.5% and 2% in clinical epidemiological studies and up to 10% in studies where thymus biopsies were reviewed.[14] Additionally, in some patients this comorbidity of SLE and thymoma was associated with poor prognosis.[16] The close interaction between these two diseases is emphasized by the observed remission of steroid therapy-resistant SLE disease following thymomectomy.[17] Notably, several manifestations of SLE have been associated with such comorbidity. In a recent meta-analysis of the link between the two diseases, the authors concluded that the possibility of thymoma should be considered and suspected among patients with late-age-onset SLE.[18] Other studies have reported polyarthritis, skin rashes, fever and cytopenias to be more common in SLE patients with thymoma.[19] Thus, it seems that although the exact mechanisms underlying both pathologies have yet to be elucidated, the association between thymoma and SLE is not incidental.[20,21] Acquired pure red cell aplasia may present as an acute self-limited disease, secondary to viral infection or drug-induced impairments, or as a chronic autoimmune form that may be associated with thymoma.[22] In the latter, damage to erythroid progenitors or precursor cells appears to be T cell-mediated,[23] and it is estimated that 5% of thymomas coexist with pure red cell aplasia.[21–23] Histological investigation of thymomas from patients diagnosed with pure red cell aplasia revealed small germinal centers and lymphoid aggregation in their bone marrow.[15] This suggests a connection between humeral and cellular alterations observed in these patients. Other immune-mediated cytopenias, such as thrombocytopenia and neutropenia, were also reported to occur in combination with thymoma.[15] The syndrome of inappropriate antidiuretic hormone secretion has been recently linked to autoimmune mechanisms[24] and thymic tumors. Several cases demonstrated syndrome of inappropriate antidiuretic hormone secretion codiagnosed with a mass lesion in the mediastinum[24] or with MG associated with thymoma;[25] however, the mechanisms underlying this connection remain to be elucidated.

Also associated with thymoma are the autoimmune bullous dermatoses-autoimmune blistering diseases, including pemphigus vulgaris, paraneoplastic pemphigus and bullous pemphigoid.[13,26] More than 20 cases of pemphigus have been documented in the past several decades,[27] and in a recent case study, the resection of thymoma resulted in regression of bullous dermatoses.[28] Other autoimmune conditions, such as polymyositis and myopathy[13,15,29] and pernicious anemia,[29]

Table 1 WHO classification of thymoma[3]

A A tumor with oval shape, with no nuclear atypia, and few or no non-neoplastic lymphocytes
AB A tumor in which foci having the features of type A thymoma are admixed with foci rich in lymphocytes
B1 A tumor that resembles the normal functional thymus in that it combines large expanses having an appearance practically indistinguishable from normal thymic cortex with areas resembling thymic medulla
B2 A tumor in which the neoplastic epithelial component appears as scattered plump cells with vesicular nuclei and distinct nucleoli among a heavy population of lymphocytes
B3 A type of thymoma predominantly composed of epithelial cells having a round or polygonal shape and exhibiting no or mild atypia
C A thymic tumor exhibiting clear-cut cytologic atypia and a set of cytoarchitectural features no longer specific to the thymus, but rather analogous to those seen in carcinomas of other organs. Type C thymomas lack immature lymphocytes

Table 2 Autoimmune diseases associated with thymoma

Disease	Remission post-tymectomy	Ref.
MG	Reduction in anti-ACH antibodies	9, 13, 46
SLE	Yes	13, 16, 17
SIADH	Yes	24, 25, 35
ARCA	Yes	13, 47, 48
BP	Yes	13, 26, 49
Others	Unknown	
Polymyositis, pernicious anemia		13, 29, 32, 35, 50, 51
Thyroiditis, hyperthyroidism		13, 29, 32, 35, 50, 51
RA, UC, DM, scleroderma		13, 29, 32, 35, 50, 51
Takayasu syndrome, Graves' disease, encephalitis		13, 29, 32, 35, 50, 51

Abbreviations: ACH, acetylcholine receptor; ACRA, acquired red cell aplasia; BP, bullous pemphigoid; DM, dermatomyositis; MG, myasthenia gravis; RA, rheumatoid arthritis; SIADH, syndrome of inappropriate antidiuretic hormone secretion; SLE, systemic lupus erythematosus; UC, ulcerative colitis.

were linked to both thymoma and MG. Less commonly, autoimmune thyroid diseases, rheumatoid arthritis, ulcerative colitis, dermatomyositis, scleroderma, Takayasu syndrome,[30] autoimmune hemolytic anemia[31] and cortical encephalitis[32] were reported. Interestingly, other thymic tumors such as thymic carcinoma related to Sjögren's syndrome[33,34] and invasive thymoma to Graves' disease[35] may also be associated with autoimmunity.

PLAUSIBLE MECHANISMS BY WHICH THYMOMA MAY INDUCE AUTOIMMUNITY

The etiology of various autoimmune diseases is perceived as a mosaic of factors that usually encompasses genetic propensity and a wide spectrum of other factors, including the environment, immune-mediated processes, infections, hormones and drugs.[36–39]. In the case of the thymus and autoimmunity, it is reasonable to speculate that a disregulation in immune function is the underlying mechanism.[40] Progenitor T cells, in a manner similar to B cells, are formed in the bone marrow; however, they later migrate to the thymus for a series of changes including maturation, differentiation and selection. Similar to B-cell maturation in the bone marrow, T-cell maturation in the thymus involves rearrangements of the germ-line T-cell receptor genes and the expression of various membrane markers. Anatomically, the thymus is composed of histologically distinct cortical and medullary areas. Upon migration to the thymus, T cells enter the outer cortex and slowly proliferate. They then progress from the outer cortex to the medullary region and complete a series of characteristic changes in their cell surface phenotype. Along with T-cell diversification and maturation into an effective repertoire of lymphocytes, an extraordinary pair of selection processes takes place in the thymus. Positive selection permits the survival of only the T cells whose T-cell receptors are capable of recognizing self-major histocompatibility complex (MHC) molecules, and it is thus responsible for the creation of a self-MHC-restricted response. Alternately, negative selection eliminates T cells that react too strongly with self-MHC or with self-MHC plus self-peptides, thus eliminating autoreactivity of these T cells.[36] These thymic functions are critical for maintaining self-tolerance and aid in the production of regulatory T cells.[37] These cells represent a specific subset of T cells that are formed either in the thymus or later at peripheral sites to dominantly control self-reactivity in the periphery. Regulatory T cells are able to suppress the activation of neighboring T cells by an autoantigen, thus inhibiting the autoimmune cascade.[38]

Based on the observations presented here, the association of thymic tumors with loss of self-tolerance is not surprising, and several mechanisms have been suggested based mainly on the assumption that the 'sick thymus' generates mature but impaired T cells.[39,41]

The immature T-cell theory

In thymoma, the epithelial and lymphoid components closely mimic the cell organization observed in normal thymus; however, thymocytes derived from thymoma may be immature and lack the sufficient self-tolerance required for normal function. This notion is supported by the observation that neoplastic cortical thymocytes exhibit antigens such as TdT^+, $T6^+$, $T4^+$ and $T8^+$, all of which are markers of immaturity. In a study by Chilosi *et al.*,[39] a comparison between normal thymus and thymoma was performed by quantitative immunostaining using a monoclonal antibody specific for Ki67, a marker of cellular proliferation. The amount of Ki67-positive cells in thymomas ranged from 35% to 80%. These levels were significantly higher than in age-matched control thymuses but were similar to those observed in thymuses from younger patients. Additionally, the amount of mature $CD4^+$ T cells in thymomas was found to be lower than in normal thymus.[42] The 'escape theory' suggests that immaturity of thymoma-derived cells results from a lack of thymocyte passage through the medullary areas in which self-tolerance is induced by dendritic cells.[43] Thus, thymoma-derived thymocytes may escape into the circulation, where they avoid critical medullary selection and maturation and thus become autoreactive.

Neoplastic–genetic theory

Another theory that attempts to explain the link between thymoma and autoimmunity is the neoplastic–genetic theory. Thymocytes acquire their antigen specificity within the thymic cortex, where the rearrangement of T-cell receptor genes takes place. In thymoma, a large portion of the cortical thymocytes are proliferating, and this high turnover rate can increase the chance of genetic mutation.[40] Interestingly, thymocytes derived from cortical areas with increased proliferation rates show self-reactivity.[44] Additionally, neoplastic epithelial cells in thymoma were found to be genetically different from those of normal control cells, because the expression of HLA-DR molecules is slightly reduced compared with expression in the normal thymus. This impaired expression of HLA-DR in neoplastic epithelial cells may affect positive selection and autoreactivity associated with HLA-A24 and HLA-B8, which are significant predictive factors for MG. In a study by Machens *et al.*,[45] these HLA subtypes were associated with increased development of thymoma. These data suggest that at least a portion of the thymic pathology that is linked to autoimmunity involves genetic aberrations.[9]

The combined cellular and humeral deregulation theory

This theory suggests a link between the adaptive arms of the immune system that allows them to act in concert to promote autoimmune disease. The export of thymoma-derived autoreactive T cells to the periphery is presumed to be a critical step in the development of thymoma-associated autoimmunity; however, an additional step has been suggested as being required to link these auto reactive T cells to autoantibody-producing B cells. Thus, a model consisting of two independent steps has been suggested.[2] The first involves a large number of thymoma-derived CD8 T cells exhibiting impaired tolerance that

initiate an autoimmune cascade. During the second step, a transformation from cellular to humoral immunity occurs through activation of CD4 T cells, which, in turn, activate B cells to produce autoantibodies. This mechanism is supported by the presence of aberrant autoimmune CD4 T cells in thymoma-associated MG, as well as association of thymoma with the presence of autoantibodies in other diseases.

CONCLUSIONS

In recent decades, a variety of autoimmune diseases other than MG have been associated with the presence of thymoma (Table 2). Although the exact mechanisms by which thymoma induces autoreactivity are yet to be elucidated, the link between the two seems to be strong and not coincidental, especially since the resection of thymoma was beneficial to patients with certain autoimmune diseases. The most probable explanation for autoimmunity related to thymoma is that the damage induced by tumor growth within the thymus diminishes its ability to maintain self-tolerance and opens a 'window of opportunity' for autoimmune diseases to develop. Elucidating these mechanisms might not only guide us in treating patients with such comorbidities but could also improve our understanding of autoimmunity and our ability to prevent this disorder.

1 Thomas CR, Wright CD, Loehrer PJ. Thymoma: state of the art. *J Clin Oncol* 1999; **17**: 2280–2289.
2 Hoffacker V, Schultz A, Tiesinga JJ, Gold R, Schalke B, Nix W *et al*. Thymomas alter the T-cell subset composition in the blood: a potential mechanism for thymoma-associated autoimmune disease. *Blood* 2000; **96**: 3872–3879.
3 Kondo K, Yoshizawa K, Tsuyuguchi M, Kimura S, Sumitomo M, Morita J *et al*. WHO histologic classification is a prognostic indicator in thymoma. *Ann Thorac Surg* 2004; **77**: 1183–1188.
4 Kondo K. Optimal therapy for thymoma. *J Med Invest* 2008; **55**: 17–28.
5 Lucchi M, Basolo F, Ribechini A, Ambrogi MC, Bencivelli S, Fontanini G *et al*. Thymomas: clinical-pathological correlations. *J Cardiovasc Surg (Torino)* 2006; **47**: 89–93.
6 Grob D, Brunner N, Namba T, Pagala M. Lifetime course of myasthenia gravis. *Muscle Nerve* 2008; **37**: 141–149.
7 Gomez AM, van den Broeck J, Vrolix K, Janssen SP, Lemmens MA, van der Esch E *et al*. Antibody effector mechanisms in myasthenia gravis—pathogenesis at the neuromuscular junction. *Autoimmunity* 2010; **43**: 353–370.
8 Soltys J, Gong B, Kaminski HJ, Zhou Y, Kusner LL. Extraocular muscle susceptibility to myasthenia gravis: unique immunological environment? *Ann NY Acad Sci* 2008; **1132**: 220–224.
9 Okumura M, Fujii Y, Shiono H, Inoue M, Minami M, Utsumi T *et al*. Immunological function of thymoma and pathogenesis of paraneoplastic myasthenia gravis. *Gen Thorac Cardiovasc Surg* 2008; **56**: 143–150.
10 Mygland A, Vincent A, Newsom-Davis J, Kaminski H, Zorzato F, Agius M *et al*. Autoantibodies in thymoma-associated myasthenia gravis with myositis or neuromyotonia. *Arch Neurol* 2000; **57**: 527–531.
11 Ghosh JB, Roy M, Peters T. Thymoma associated with myasthenia gravis in infancy. *Indian J Pediatr* 2009; **76**: 1057–1058.
12 Chen X, Fang L, Song S, Guo TB, Liu A, Zhang JZ. Thymic regulation of autoimmune disease by accelerated differentiation of Foxp3$^+$ regulatory T cells through IL-7 signaling pathway. *J Immunol* 2009; **183**: 6135–6144.
13 Shere Y, Bar-Dayan Y, Shoenfeld Y. Tymoma thymic hyperplasia, thymectomy and autoimmune diseases. *Int J Oncol* 1997; **10**: 939–943.
14 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**: 1044–1046.
15 Souadjian JV, Enriquez P, Silverstein MN, Pepin JM. The spectrum of diseases associated with thymoma. Coincidence or syndrome? *Arch Intern Med* 1974; **134**: 374–379.
16 Rosman A, Atsumi T, Khamashta MA, Ames PR, Hughes GR. Development of systemic lupus erythematosus after chemotherapy and radiotherapy for malignant thymoma. *Br J Rheumatol* 1995; **34**: 1175–1176.
17 Zandman-Goddard G, Lorber M, Shoenfeld Y. Systemic lupus erythematosus and thymoma—a double-edged sword. *Int Arch Allergy Immunol* 1995; **108**: 99–102.
18 Zhang L, Dong J, Leng XM, Zeng XF. A meta-analysis of thymoma-associated systemic lupus erythematosus from 1975–2008 worldwide. *Zhonghua Nei Ke Za Zhi* 2009; **48**: 643–646. Chinese.
19 Park MJ, Kim YA, Lee SS, Kim BC, Kim MK, Cho KH. Appearance of systemic lupus erythematosus in patients with myasthenia gravis following thymectomy: two case reports. *J Korean Med Sci* 2004; **19**: 134–136.
20 Mevorach D, Perrot S, Buchanan NM, Khamashta M, Laoussadi S, Hughes GR *et al*. Appearance of systemic lupus erythematosus after thymectomy: four case reports and review of the literature. *Lupus* 1995; **4**: 33–37.
21 Bozzolo E, Bellone M, Quaroni N, Voci C, Sabbadini MG. Thymoma associated with systemic lupus erythematosus and immunologic abnormalities. *Lupus* 2000; **9**: 151–154.
22 Gaman A, Gaman G, Bold A. Acquired aplastic anemia: correlation between etiology, pathophysiology, bone marrow histology and prognosis factors. *Rom J Morphol Embryol* 2009; **50**: 669–674.
23 Thompson CA, Steensma DP. Pure red cell aplasia associated with thymoma: clinical insights from a 50-year single-institution experience. *Br J Haematol* 2006; **135**: 405–407.
24 Galesic K, Krizanac S, Vrkljan M, Ljubanovic D. Syndrome of inappropriate secretion of antidiuretic hormone due to malignant thymoma. *Nephron* 2002; **91**: 752–754.
25 Donadio AC, Dragnev KH, Schwartz GK. Thymoma associated with syndrome of inappropriate antidiuretic hormone secretion and myasthenia gravis. *South Med J* 1998; **91**: 278–279.
26 Mutasim DF. Autoimmune bullous dermatoses in the elderly: an update on pathophysiology, diagnosis and management. *Drugs Aging* 2010; **27**: 1–19.
27 Souteyrand P, Berthier-Boachon M, Thivolet J. Pemphigus and thymoma: review and etiopathogenesis (author's transl). *Ann Dermatol Venereol* 1981; **108**: 457–467. French.
28 Barbetakis N, Samanidis G, Paliouras D, Boukovinas I, Asteriou C, Stergiou E *et al*. Paraneoplastic pemphigus regression after thymoma resection. *World J Surg Oncol* 2008; **6**: 83.
29 Davila DG, Ryan DH. Thymoma, hypogammaglobulinemia, and pernicious anemia. *South Med J* 1986; **79**: 904–906.
30 Elliott GB, Hill M, Howard DL. Whipple's disease associated with benign thymoma. *Can Med Assoc J* 1961; **85**: 1340–1344.
31 de Keyzer K, Peeters P, Verhelst C, Dendooven A, Vonck A, Vanholder R. Autoimmune haemolytic anaemia associated with a thymoma: case report and review of the literature. *Acta Clin Belg* 2009; **64**: 447–451.
32 Hammoud K, Kandimala G, Warnack W, Vernino S. Multifocal paraneoplastic cortical encephalitis associated with myasthenia gravis and thymoma. *Arch Neurol* 2009; **66**: 1407–1409.
33 Arbib F, Bejui F, Bouvier R, Ninet J, Guerin JC. Thymoma and primary Gougerot–Sjogren syndrome progressing to severe bronchiolitis. *Rev Mal Respir* 1993; **10**: 465–467. French.
34 Yoshida H, Matsuda S, Abe R, Kimura H, Shichishima T, Tanaka T *et al*. Sjogren's syndrome associated with a benign thymic tumor: report of a case with wide spectrum of clinical feature (author's transl). *Nippon Ketsueki Gakkai Zasshi* 1980; **43**: 834–841. Japanese.
35 Lee BW, Ihm SH, Shin HS, Yoo HJ. Malignant thymoma associated with myasthenia gravis, Graves' disease, and SIADH. *Intern Med* 2008; **47**: 1009–1012.
36 Kabelitz D, Schreiber S. Autoimmunity. Physiological control mechanisms and pathways to autoimmune disease. *Internist (Berl)* 2009; **50** : 267–275. German.
37 Wang L. Adaptive Treg generation by DCs and their functional analysis. *Methods Mol Biol* 2010; **595**: 403–412.
38 Wing K, Sakaguchi S. Regulatory T cells exert checks and balances on self tolerance and autoimmunity. *Nat Immunol* 2010; **11**: 7–13.
39 Chilosi M, Iannucci A, Menestrina F, Lestani M, Scarpa A, Bonetti F *et al*. Immunohistochemical evidence of active thymocyte proliferation in thymoma. Its possible role in the pathogenesis of autoimmune diseases. *Am J Pathol* 1987; **128**: 464–470.
40 Shoenfeld Y, Lorber M, Yucel T, Yazici H. Primary antiphospholipid syndrome emerging following thymectomy for myasthenia gravis: additional evidence for the kaleidoscope of autoimmunity. *Lupus* 1997; **6**: 474–476.
41 Vincent A, Willcox N. The role of T-cells in the initiation of autoantibody responses in thymoma patients. *Pathol Res Pract* 1999; **195**: 535–540.
42 Tokunaga T, Hayashi A, Kadota Y, Shiono H, Inoue M, Sawabata N *et al*. Regulation of Th-POK and Runx3 in T cell development in human thymoma. *Autoimmunity* 2009; **42**: 653–660.
43 Kyewski BA. Thymic dendritic cells present blood-borne antigens to medullary thymocytes *in vivo*: a possible role in the generation of the T-cell repertoire. *Haematol Blood Transfus* 1985; **29**: 486–491.
44 Theofilopoulos AN, Dummer W, Kono DH. T cell homeostasis and systemic autoimmunity. *J Clin Invest* 2001; **108**: 335–340.
45 Machens A, Loliger C, Pichlmeier U, Emskotter T, Busch C, Izbicki JR. Correlation of thymic pathology with HLA in myasthenia gravis. *Clin Immunol* 1999; **91**: 296–301.