

Human Leukocyte Antigen (HLA) Subtype-Dependent Development of Myasthenia Gravis, Type-1 Diabetes Mellitus, and Hashimoto Disease: A Case Report of Autoimmune Polyendocrine Syndrome Type 3

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Conflict of interest: None declared

Patient: Female, 40
Final Diagnosis: Autoimmune polyendocrine syndrome type 3
Symptoms: Thirst • polyuria • weight-loss
Medication: —
Clinical Procedure: —
Specialty: Endocrinology and Metabolic





Objective: Rare co-existence of disease or pathology
Background: Patients with type 1 diabetes mellitus, myasthenia gravis (MG), and Hashimoto disease are diagnosed as having autoimmune polyendocrine syndrome type 3 (APS3). APS3 is rare, and its pathogenesis is unclear. We describe a female patient with APS3 whose human leukocyte antigen (HLA) type could provide a clue to the pathogenesis of APS3.

Case Report: A 40-year-old Japanese female patient who had been diagnosed with MG at 5 years of age, and which had been treated with cholinesterase inhibitors, was referred to our hospital with thirst, polydipsia, polyuria, weight loss, and hyperglycemia. She was found to have type 1 diabetes mellitus based on laboratory tests. She was also positive for anti-thyroid peroxidase antibody and was thus diagnosed with Hashimoto disease. This combination of type 1 diabetes mellitus, myasthenia gravis, and Hashimoto disease led to a diagnosis of APS3. Her HLA serotype was A24; B46/54; DR4/9; DQ8/9, and genotype was A*24: 02; B*46: 01: 01/54: 01: 01; C*01: 02; DRB1*04: 06/09: 01: 02; DQB1*03: 02: 01/03: 03: 02; and DQA1*03: 01/03: 02: 01. We subsequently reviewed 10 cases of APS3 combined with MG, including the present case and cases reported in Japanese. This review revealed that HLA-DR9/DQ9 might be a specific HLA subtype associated with APS3 with MG. Four of the 10 cases had MG diagnosed before diabetes mellitus and autoimmune thyroid disease.

Conclusions: The present case showed that, in people with HLA-B46 and -DR9, antibody-negative MG can precede the development of APS3 by many years. Physicians should consider the possibility of APS3 when evaluating patients with ocular-type myasthenia gravis, and screen them for type 1 diabetes.

MeSH Keywords: Autoimmune Diseases • Diabetes Mellitus • Hashimoto Disease • HLA Antigens • Myasthenia Gravis • Polyendocrinopathies, Autoimmune

Full-text PDF: <https://www.amjcaserep.com/abstract/index/idArt/918996>

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Background

Autoimmune polyendocrine syndrome type 3 (APS3) consists of multiple autoimmune diseases, including autoimmune thyroid disorders (AITD), type-1 diabetes mellitus (T1DM), lymphocytic hypophysitis, insulin autoimmune syndrome, and pernicious anemia, all of which are related to the loss of immune tolerance [1,2]. The absence of adrenocortical dysfunction is one of the features that distinguishes APS3 from the autoimmune polyendocrine syndrome types 1 and 2 [3].

Myasthenia gravis (MG) is classified as an autoimmune disease, as are T1DM and AITD, and HLA-B46/-DR9 has been reported to be associated with early-onset ocular subtype [4]. Although APS3 accounts for 41.5% of all autoimmune polyendocrine syndromes [2], we found only 2 case reports on APS3 combined with MG [5,6] through a PubMed search. Although the patients' clinical features, such as disease-specific HLA, typical manner of onset, and clinical types, were reported, the small number of case reports has provided limited insights on APS3 combined with MG. For example, although some cases of MG and T1DM are associated with the same HLA type, it remains unknown whether these conditions develop interdependently or whether their occurrence is not associated. In addition, it remains unknown whether measurement of anti-islet antibodies provides clues to the prognosis of T1DM and whether thymus resection can prevent the development of T1DM. Answers to these questions could provide a better understanding of the pathogenesis of APS3. This could help physicians to provide appropriate treatment for patients with this condition.

After extending our literature search to Japan Medical Abstracts Society, we found additional 7 published case reports on APS3 with MG. These additional reports were either written in Japanese or presented at conferences held in Japan [7]. The fact that we were able to identify this many additional cases by searching a localized database suggests that APS3 complicated by MG might not be as rare as current estimates suggest, leading us to investigate the clinical features and underlying pathology characterizing APS3 with MG.

This study was approved by the Institutional Review Board of Kurume University Hospital (2019-021), and all procedures were in accordance with its ethical standards, and with the principles of the 2013 Declaration of Helsinki. Written informed consent for publication of the patient's clinical details and clinical images was obtained from the patient.

In this report, we describe a case of APS3 complicated by MG and compare the onset-type, clinical sub-types, and autoantibody-titers for each disease, and compare our patient's case with the features of 9 other cases that have been reported previously. The objective was to gain a better understanding

of the pathogenesis of APS3 in order to make recommendations about its treatment. Furthermore, having identified novel HLA subtypes during the course of our analysis, we expanded the aims of our study to include an assessment of APS3 with MG about its specific clinical features.

Case Report

A 40-year-old Japanese female patient was referred to our endocrinology and metabolism center at a university hospital with complaints of thirst, polyuria, and a 6-kg weight-loss in the previous 3 months. Her history revealed an appendectomy at 10 years of age and treatment for Guillain-Barré syndrome at 25 years of age. She had been diagnosed with MG at 5 years of age, which was treated with cholinesterase inhibitors. She showed hyperglycemia on admission (Table 1), although she did not report having had symptoms of diabetes mellitus during the previous year. She reported that she had a nephew with T1DM. On physical examination, all of her deep tendon reflexes were absent; however, manual muscle testing of her extremities revealed that her muscle strength was normal (5/5). She had bilateral ptosis, a positive Tensilon test, and ophthalmoplegia when gazing in all directions, causing double vision.

Although blood gas analysis did not reveal metabolic acidosis, she had hyperglycemia, high hemoglobin A1c, and was positive for anti-glutamic acid decarboxylase antibody, and urinary ketones (Table 1). The tests for acetylcholine receptor antibodies and muscle-specific kinase antibodies, autoantibodies associated with MG, were negative. The positive result for anti-thyroid peroxidase antibody (Table 1), and the heterogeneous echo-pattern of thyroid gland (Figure 1) lead to diagnosis of Hashimoto disease [8] without thyroid dysfunction. The computed tomography did not show enlargement of thymus gland and atrophy of pancreas (Figure 2). The glucagon-loading examination found that her insulin secretion was diminished, but not absent [9]. Her adrenal function was normal, and no abnormalities were found on gastro-duodenoscopy.

We diagnosed her with APS3 [1,2], which was consistent with her acute-onset T1DM and diabetic ketosis without acidosis, euthyroid Hashimoto disease, and MG (Table 2). Her doses of insulin and cholinesterase were adjusted, but no therapy was provided for her Hashimoto disease. Her HLA type is described in Table 3. When she was last followed up 6 months after diagnosis, her diabetes was well controlled with a combination of insulin injections and suitable diet. Her MG was controlled with cholinesterase inhibitors, with mild ophthalmoplegia showing no change during the follow-up period.

Table 1. Laboratory findings on admission.

Test	Value	Reference range	Test	Value	Reference range
Urinalysis			Endocrinology		
Sugar	++++	-	Glucose, mg/dL	182	73–109
Ketone	+	-	HbA1c, %	10.0	4.9–6.0
Venous blood gas analysis			TSH, μ U/mL	1.39	0.5–5.0
pH	7.367	7.35–7.45	Free-T3, pg/mL	2.2	2.3–4.0
pCO ₂ , mmHg	46.1		Free-T4, ng/dL	1.13	0.93–1.70
pO ₂ , mmHg	21.0		Immunology		
HCO ₃ , mmol/L	25.9		CRP, mg/dL	<0.04	≤0.14
Blood chemistry			Anti-GAD Ab, U/mL	>2000	5.0
BUN, mg/dL	15	8–20	Anti-IA2 Ab, U/mL	<0.4	<0.4
Cr, mg/dL	0.61	0.46–0.79	Anti-Tg Ab, IU/mL	<10	<28
Na, mmol/L	137	138–145	Anti-TPO Ab, IU/mL	86	<16
K, mmol/L	3.9	3.6–4.8	TS Ab, %	3.6	<15.0
Cl, mmol/L	101	101–108	TR Ab, IU/L	<2.0	<2.0
AST, IU/L	17	13–30	Anti-Ach-R Ab, nmol/L	≤0.2	≤0.2
ALT, IU/L	17	7–30	Anti-MUSK Ab, nmol/L	<0.01	≤0.02
CK, U/L	43	41–153			
Amylase, U/L	111	44–132			

Ach-R Ab – acetylcholine receptor antibody; GAD Ab – glutamic acid decarboxylase antibody; IA2 – insulinoma-associated antigen-2; MUSK Ab – muscle-specific kinase antibody; T3 – triiodothyronine; T4 – thyroxine; Tg Ab – thyroglobulin antibody; TPO Ab – thyroid peroxidase antibody; TR Ab – thyrotropin receptor antibody; TS Ab – thyroid stimulating antibody.

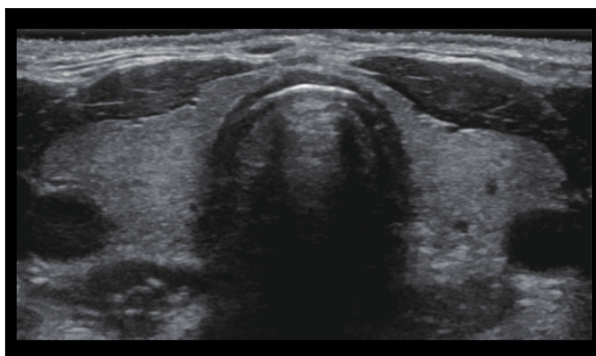


Figure 1. Cervical ultrasonography examination of the present case. The thyroid gland shows a mild heterogeneous echo pattern and diffuse enlargement. The right left lobes 15.2×46.3×11.0 mm and 15.6×36.5×9.9 mm in dimension, respectively, and 4.1 cm³ and 3.0 cm³ in volume, respectively.

Case comparisons

The features of the 9 cases reported previously, and the present case, are summarized in Tables 2 and 3. We compared the clinical features and HLA haplotypes of the cases included in

our case review to those previously described in the general Japanese population [10] and to those of other cases of MG, T1DM, and Hashimoto disease described in the literature [5–7].

The frequencies were compared using Fisher's exact test. *P*-values <0.05 were considered statistically significant. All statistical analyses were performed using GraphPad Prism 7.0.4 (GraphPad Software, CA, USA).

The frequency of ocular-type MG in this case series was significantly higher than that of patients with MG described in a previous report (90% [9/10 cases] versus 20%, *P*<0.001) [11]. In this study, T1DM progressed to AITD more frequently in patients with AITD and T1DM without MG (50.0% [5/10 cases] versus 7.1% [1/14 cases], *P*=0.028) [12]. In addition, the prevalence of slowly progressive, insulin-dependent diabetes mellitus (SPIDDM) in this study was lower than that reported in patients with AITD and T1DM without MG (30.0% [3/10 cases] versus 71.4% [10/14 cases], *P*=0.055) [12].

The prevalence of HLA-DR9 in APS3 patients with MG was higher than that of the general Japanese population (75.0% [6/8 cases] versus 14.283%, *P*<0.001) [10], although the present

Table 2. Characteristics of the cases of type-1 diabetes mellitus with myasthenia gravis and autoimmune thyroid disease.

Case No. [ref]	Sex	Age at onset			First condition diagnosed	MG type	T1DM onset-type	Type of AITD
		MG	T1DM	AITD				
1 [5]	F	51	51	47	AITD	General type	Unknown	HD
2 [6]	M	37	NA	37	T1DM	Ocular type	Unknown	HD
3 [7]	M	64	59	NA	Unknown	Ocular type+ dysphagia	Acute onset	HD
4 [7]	M	31	37	30	MG	Ocular type	Acute onset	GD
5 [7]	M	27	32	33	MG	Ocular type	SPIDDM	GD
6 [7]	F	27	35	27	MG+AITD	Ocular type	SPIDDM	GD
7 [7]	F	29	19	19	T1DM+AITD	Ocular type	Acute onset	GD
8 [7]	M	37	43	37	MG+AITD	Ocular type+ upper limb	SPIDDM	GD
9 [7]	F	10	15	35	MG	Ocular type	Acute onset	GD
Present case	F	6	40	40	MG	Ocular type	Acute onset	HD

AITD – autoimmune thyroid disease; GD – Graves’ disease; HD – Hashimoto disease; MG – myasthenia gravis; NA – not applicable; SPIDDM – slowly progressive insulin-dependent diabetes mellitus; T1DM – type 1 diabetes mellitus.

Table 3. Autoantibody profile, thymic pathology, HLA serotype, and genotype of the cases of type-1 diabetes mellitus with myasthenia gravis and autoimmune thyroid disease.

Case No. [ref]	Autoantibody, U/mL			Thymus gland (pathology, surgery)	HLA-typing (serotype; genotype)
	Ach-R	GAD	IA2		
1 [5]	>8.0	182	1,815	Hyperplasia, resected	DQ2 and DQ8 absent; NA
2 [6]	–	NA	NA	Normal	NA; NA
3 [7]	29	2,200	NA	Malignant thymoma, resected	A2/24(9), B51(5)/59, Cw1, DR4; NA
4 [7]	+	31.3	NA	Thymoma, resected	DR9; DQB1*0303(+)
5 [7]	1.8	62	NA	NA, resected	DR9/5(6); DQA1*03: 01/0101_02, DQB1*03: 03/06: 04
6 [7]	–	>256	NA	NA	A31 (19)/33 (19), B51 (5)/44 (12), Cw1-7: not detected, DR6/9; NA
7 [7]	–	+	NA	NA	A2/11, B54(22)/61(40), Cw1/3, DR4/9, DQ3/4; NA
8 [7]	–	399	–	NA, resected	NA; DRB1*08: 02: 01/15: 01: 01, DQB1*03: 02: 01/06: 02, DQA1*01: 02/04: 01
9 [7]	0.8	241	NA	Hyperplasia, resected	NA; DRB1*09: 01: 02/13: 02: 01, DQB1*03: 03: 02/06: 04: 01
Present case	–	>2,000	<0.4	Normal	A24/24, B46/54, DR4/9, DQ8/9; A*24: 02, B*46: 01: 01/54: 01: 01, C*01: 02, DRB1*04: 06/09: 01: 02, DQB1*03: 02: 01/03: 03: 02, DQA1*03: 01/03: 02: 01

Ach-R – acetylcholine receptor; GAD – glutamic acid decarboxylase; HLA – human leukocyte antigen; IA2 – insulinoma-associated antigen-2; NA – not available.

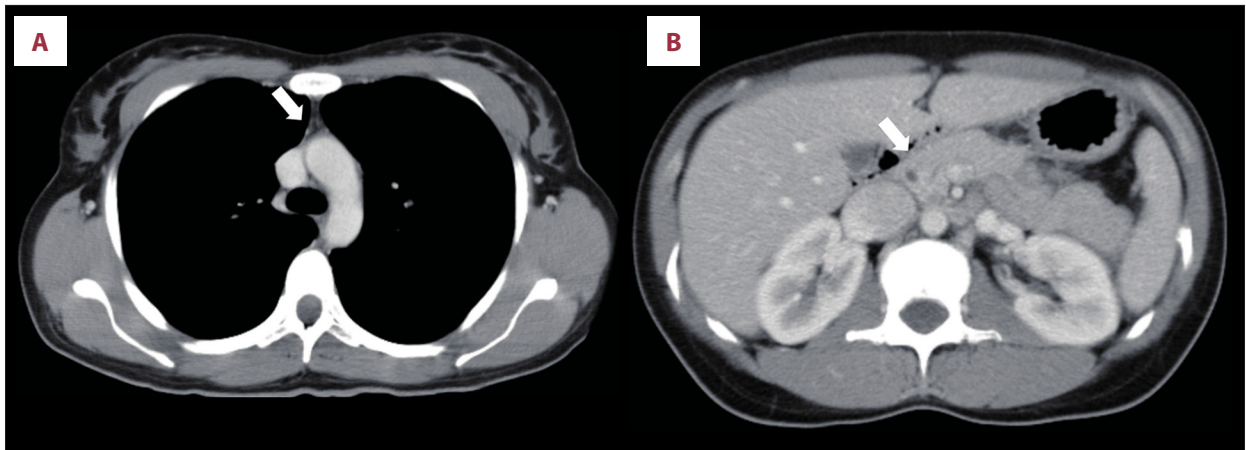


Figure 2. Chest contrast computed tomography imaging of the present case. (A) There is no evidence of a thymoma (arrow); and (B) the size of the pancreas is normal (arrow).

case was the only case with HLA-B46. In addition, the prevalence of the HLA-DQ9 type had a significantly higher prevalence among cases in our study than among Japanese bone marrow donors (57.1% [4/7 cases] versus 16.1%, $P=0.016$) [13]. In contrast, the frequency of HLA-DR4, which has been reported to be associated with T1DM [14], was similar to that of the general Japanese population (37.5% [3/8 cases] versus 23.879%, $P=0.29$).

Discussion

We described a case who diagnosed with APS3, including T1DM, AITD, and early-onset seronegative ocular MG. HLA-B46-DR9: B*46: 01-DRB1*09: 01 represent high prevalence in early-onset ocular MG [4]. However, the present case is the first case to be described with HLA-B46/DR9: B*46: 01-DRB1*09: 01, early-onset ocular MG, T1DM, and AITD, as APS3 (Tables 2, 3).

Previously, the HLA-DR9 has been associated with the ocular type of MG, and seronegative MG [15]. In addition, HLA-DR9/DQ9 and DR4 have previously been reported to be associated with T1DM [14]. Taking account for the results of this study into account, HLA-DR9/DQ9 may be a specific HLA subtype associated with APS3 with a combination of MG, T1DM, and AITD. In contrast, the frequency of HLA-DR4, which is a sensitive HLA subtype for T1DM and was positive in the present case [14], is similar to that of the general Japanese population [13]. The findings of this study suggest that MG complicated with APS3 might be associated with the ocular-type of MG, because the frequency of ocular-type of MG in this study was significantly higher than that of all cases of MG described in a previous report [11]. Notably, HLA-B46/DR9: B*46: 01-DRB1*09: 01, which was only found in the present case, may independently associated with early-onset ocular MG [4] as APS3.

As shown by the present case, T1DM complicated with MG might be the acute onset-type. Most of the cases of T1DM and AITD, but without MG, have the SPIDDM type of T1DM [2,12] and develop after the onset of AITD. However, we found that among the cases of APS3 with MG included in this review, the diagnosis of T1DM more frequently preceded the development of AITD and was more frequently the acute-onset type, compared to patients with ordinary T1DM without MG [12]. Acute-onset T1DM and SPIDDM are both considered autoimmune conditions [12]. Furthermore, both forms of T1DM are associated with the presence of anti-islet antibodies, and a high prevalence of HLA-DR4 and -DR9 [14]. Although the mechanisms underlying the differences between the 2 forms are not understood, the conditions are distinct in terms of the age of onset, islet autoantibody titer, and residual beta-cell function at onset [16]. The acute onset of T1DM in the present case might provide clues to the pathogenesis of T1DM and its mechanism of progression.

Moreover, these new insights regarding T1DM might have consequences for recommended treatments. Thymectomy might be ineffective for preventing the development of T1DM although it has become one of the primary therapies used to improve the neurological functioning in patients with MG. Furthermore, the latest research has shown that the thymectomy is effective for generalized MG without thymoma [17]. However, the therapeutic effect of thymectomy for the ocular type and seronegative MG has not been shown yet. Immunologic tolerance is established by the central tolerance that removes autoreactive T-cells during the maturation process in the thymus, and peripheral tolerance by which regulatory T-cells in the peripheral tissues inhibit autoreactive T-cells. Dysfunction of immunologic tolerance leads to various autoimmune diseases, including T1DM [18]. T1DM has recently been reported to be associated with failure of peripheral immunologic tolerance as a result of dysfunction of the regulatory T-cells [19], but

the mechanism remains to be clarified. However, there is relatively little information available on the association of T1DM with central immunologic tolerance failure, and research on the association between immunologic tolerance and T1DM has been based on animal studies in which non-obese diabetic mice were used [20,21].

The main limitation of the present study the small number of cases included in the review. The numbers are insufficient to determine whether the HLA-DR9/DQ9 serotypes are specific predictors for development of APS3 with MG. Although one previous case report of T1DM that developed after thymectomy was reported [22], further evidence is necessary to determine whether thymectomy may prevent the development of T1DM.

Conclusions

HLA-DR9/DQ9 might be specific HLA serotypes associated with the APS3 subtype with both MG and T1DM. In our patient's case, her T1DM was the acute-onset type and developed many

years after the onset of MG, which differed from the more common presentation of T1DM with AITD as SPIDDM. The examination of anti-islet antibody with ocular-type MG patients with the HLA-DR9/DQ9 serotype might help to assess the risk of developing T1DM.

Department and Institution where work was done

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Conflicts of interest

None.

Abbreviations

AITD – autoimmune thyroid disorder; APS – autoimmune polyendocrine syndrome; HLA – human leukocyte antigen; MG – myasthenia gravis; SPIDDM – slowly progressive insulin-dependent diabetes mellitus; T1DM – type 1 diabetes mellitus.

References:

1. Cutolo M: Autoimmune polyendocrine syndromes. *Autoimmun Rev*, 2014; 13: 85–89
2. Kahaly GJ, Frommer L: Polyglandular autoimmune syndromes. *Eur J Endocrinol*, 2009; 161: 11–20
3. Husebye ES, Anderson MS, Kämpe O: Autoimmune polyendocrine syndromes. *N Engl J Med*, 2018; 378: 1132–41
4. Feng HY, Yang LX, Liu WB et al: The HLA-B*4601-DRB1*0901 haplotype is positively correlated with juvenile ocular myasthenia gravis in a southern Chinese Han population. *Neurol Sci*, 2015; 36: 1135–40
5. De Marchi SU, Cecchin E, De Marchi S: Autoimmune spontaneous chronic urticaria and generalized myasthenia gravis in a patient with polyglandular autoimmune syndrome type 3. *Muscle Nerve*, 2015; 52: 440–44
6. Briscoe NK, Mezei MM: Polyglandular autoimmune syndrome type 3 in a patient with ocular myasthenia gravis. *Muscle Nerve*, 2009; 40: 1064–65
7. Gobaru M, Ashida K, Nasu-Yoshinobu S et al: Supplemental Table from: The reference list of case reports on autoimmune polyendocrine syndrome type 3 with myasthenia gravis, which were either written in Japanese or presented at conferences held in Japan. *Figshare Repository* 2011. Deposited 23 July 2019. <https://doi.org/10.6084/m9.figshare.8982413.v1>
8. Caturegli P, De Remigis A, Rose NR: Hashimoto thyroiditis: clinical and diagnostic criteria. *Autoimmun Rev*, 2014; 13: 391–97
9. Faber OK, Binder C: C-peptide response to glucagon. A test for the residual beta-cell function in diabetes mellitus. *Diabetes*, 1977; 26: 605–10
10. Ikeda N, Kojima H, Nishikawa M et al: Determination of HLA-A, -C, -B, -DRB1 allele and haplotype frequency in Japanese population based on family study. *Tissue Antigens*, 2015; 85: 252–59
11. Sieb JP: Myasthenia gravis: An update for the clinician. *Clin Exp Immunol*, 2014; 175: 408–18
12. Osaki Y, Kawai K, Motohashi S et al: Type 1 diabetes mellitus and autoimmune thyroid disease in Japanese: Prevalence and pattern of onset. *J Jpn Diab Soc*, 2009; 52: 887–93
13. Japanese Society for Histocompatibility and Immunogenetics. [The HLA frequency list of donors for bone marrow transplantation in Japan] <http://jsh.umin.ac.jp/standardization/file/JSHI-hyokiallele-2019list.pdf> [in Japanese]
14. Kawabata Y, Ikegami H, Awata T et al: Differential association of HLA with three subtypes of type 1 diabetes: Fulminant, slowly progressive and acute-onset. *Diabetologia*, 2009; 52: 2513–21
15. Shinomiya N, Nomura Y, Segawa M: A variant of childhood-onset myasthenia gravis: HLA typing and clinical characteristics in Japan. *Clin Immunol*, 2004; 110(2): 154–58
16. Kobayashi T, Tamemoto K, Nakanishi K et al: Immunogenetic and clinical characterization of slowly progressive IDDM. *Diabetes Care*, 1993; 16: 780–88
17. Wolfe GI, Kaminski HJ, Aban IB et al: Randomized trial of thymectomy in myasthenia gravis. *N Engl J Med*, 2016; 375: 511–22
18. Theofilopoulos AN, Kono DH, Baccala R: The multiple pathways to autoimmunity. *Nat Immunol*, 2017; 18(7): 716–24
19. Hull CM, Peakman M, Tree TIM: Regulatory T cell dysfunction in type 1 diabetes: What's broken and how can we fix it? *Diabetologia*, 2017; 60: 1839–50
20. Mendes-da-Cruz DA, Smaniotto S, Keller AC et al: Multivectorial abnormal cell migration in the NOD mouse thymus. *J Immunol*, 2008; 180: 4639–47
21. Mendes-da-Cruz DA, Lemos JP, Passos GA, Savino W: Abnormal T-cell development in the thymus of non-obese diabetic mice: possible relationship with the pathogenesis of Type 1 Autoimmune Diabetes. *Front Endocrinol (Lausanne)*, 2018; 9: 381
22. Masuzawa M, Uechi E, Matsuda M, Motojima S: [A case of type 1 diabetes mellitus with impaired cell-mediated immunity after the resection of thymoma.] *J Jpn Diab Soc*, 2008; 51: 1093–98 [in Japanese]