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Case Report

Autoimmune polyglandular syndrome type III which accompanies to multiple sclerosis: A case report

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Abstract

Autoimmune polyglandular syndrome type III (APS III) is characterised by autoimmune destruction of various endocrine and non-endocrine tissues. It differs from APS I and APS II in terms of without adrenal involvement. Although APS III includes a series of autoimmune disorders, it is rarely associated with multiple sclerosis (MS). A 41-year-old female patient had diplopia, visual blurring, dizziness, and giddiness for 2 weeks. In her medical history, she had a diagnosis of MS and using Teriflunomide. It was detected positivity of antinuclear antibody (ANA), anti-thyroid peroxidase (Anti-TPO) and anti-thyroglobulin (Anti-TG) antibodies. Based on these results, the patient with MS who has chronic autoimmune thyroiditis and primary ovarian failure was diagnosed with APS III. The coexistence of APS-III and MS is a rare clinical entity. Moreover, hypothyroidism has been detected during teriflunomide therapy in the patient. Hypothyroidism was most likely a component of APS-III in our case, but it may also have been triggered by teriflunomide.

Keywords: Autoimmune polyglandular syndrome (APS) type III; multiple sclerosis; teriflunomide

INTRODUCTION

Autoimmune polyglandular syndromes (APSs) that mainly lead to hypofunction of multiple endocrine glands are a group of immune-mediated diseases. In 1980, Neufeld and Blizzard have developed the first classification of polyglandular failure (1). According to this, APS I is composed of adrenal insufficiency, hypoparathyroidism, and candidiasis of the skin and mucous membranes. APS II is consisted from coexistence of adrenal insufficiency, autoimmune thyroid disease and type 1 diabetes mellitus. Unlike APS I and II, APS III which does not cause adrenal insufficiency is defined by the presence of an autoimmune thyroid disease and other autoimmune disorders. It can be further divided into three subcategories: APS IIIA — autoimmune thyroiditis with type 1 diabetes mellitus; APS IIIB — autoimmune thyroiditis with pernicious anemia; and APS IIIC — autoimmune thyroiditis with vitiligo and/or alopecia and/or another organ-specific autoimmune disease (2).

Multiple sclerosis (MS) is a common neurologic disease that is characterised by demyelination of white matter in the central nervous system (CNS). Although its etiology is still unknown, the current view is that MS is probably an immune-mediated disorder for which a genetic predisposition exists to some triggers in the environment, such as benign viral infections. Pathologically, focal-often perivascular-areas of demyelination with reactive gliosis are found scattered in the white matter of brain and spinal cord and in the optic nerves (3). The demyelination areas which is also called plaques of MS can be detected by magnetic resonance imaging (MRI). The clinical manifestations depend on the areas of the nervous system involved. Optic neuritis is one of the most important presentations. The patients with MS have episodic neurologic symptoms including weakness, numbness, paresthesias, diplopia, ataxia, vertigo, sensory loss and visual blurring. The course of the disease can be relapsing-remitting or progressive. Neither definitive diagnostic test nor absolute treatment for MS are not

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exist yet. Understanding the immunopathogenesis of MS has led to the development of specific therapies aimed at intervening at different points in the autoimmune process.

Teriflunomide is one of the new immunomodulatory drugs which is developed for treatment of MS in recent years. It is the active metabolite of leflunomide that is an approved therapy for rheumatoid arthritis (4). The ability to noncompetitively and reversibly inhibit the mitochondrial enzyme dihydro-orotate dehydrogenase, relevant for the de novo synthesis of pyrimidine, is believed to exert the most important therapeutic effect (5). The inhibition of this enzyme by teriflunomide leads to a cytostatic impact on peripheral T- and B-lymphocytes. In addition, teriflunomide inhibits protein tyrosine-kinase activity, reducing T-cell proliferation, activation, and production of cytokines (6). This presumably decreases the number of activated lymphocytes that enter the CNS, thereby decreasing the inflammatory response known to be present in the CNS in patients with MS. In contrary to other immunomodulatory drugs such as interferon β and alemtuzumab which are used for treatment of MS, the existence of any autoimmune disorder that is probably related with teriflunomide therapy is an unusual clinical condition. Therefore, we present this case with autoimmune thyroiditis who is detected overt hypothyroidism after teriflunomide treatment.

CASE REPORT

A 41-year-old female patient had recourse to Ophthalmology and Neurology departments of our hospital because she had diplopia, visual blurring, dizziness, and giddiness for 2 weeks. In her medical history, there were numbness on left arm and left leg 2 years ago and visual blurring on right eye 2 months ago.

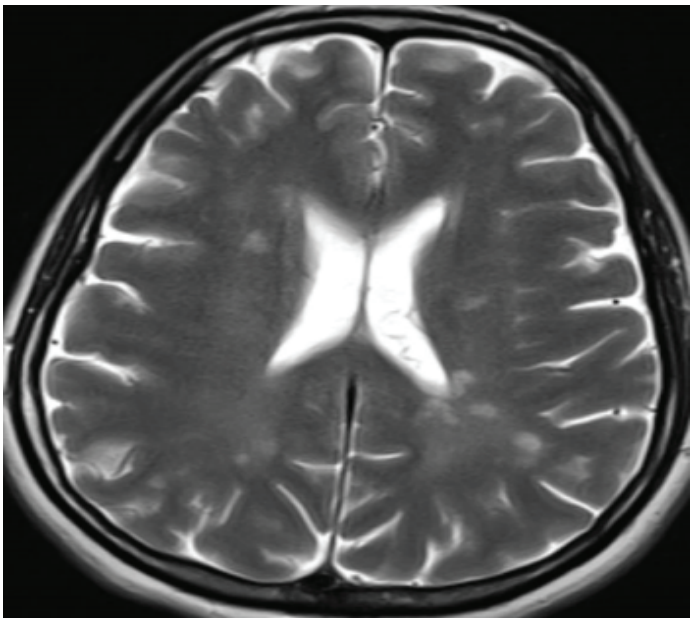

Figure 1. Brain magnetic resonance imaging of the patient. Multiple demyelinating plaques on axial T2-weighted image

The patient stated that both of these complaints had improved spontaneously in a few weeks. Additionally, she reported cessation of menstrual cycle at the age of 39. It was not detected any remarkable finding except decreased visual acuity (20/25) of right eye in ophthalmological examination and mild hypoesthesia involved the left upper and lower limbs in neurological examination. Numerous demyelinating plaques in various localisations of CNS such as, periventricular area, corona radita, centrum semiovale, right brachium pontis, right temporal and occipital lobes, and craniocervical junction was detected on MRI (Figure 1-2-3).

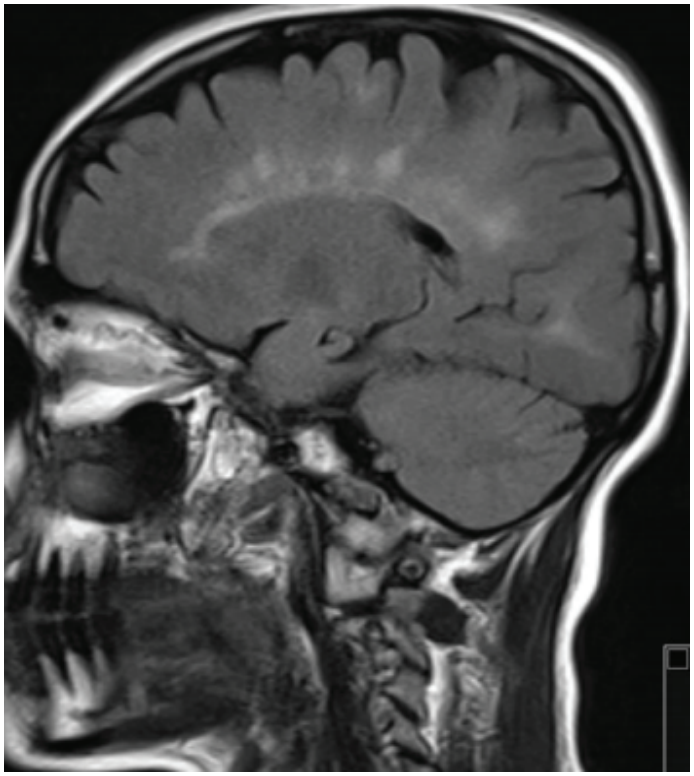

Figure 2. Demyelinating plaques on brain magnetic resonance imaging. Sagittal section image with FLAIR (Fluid-attenuated inversion recovery)

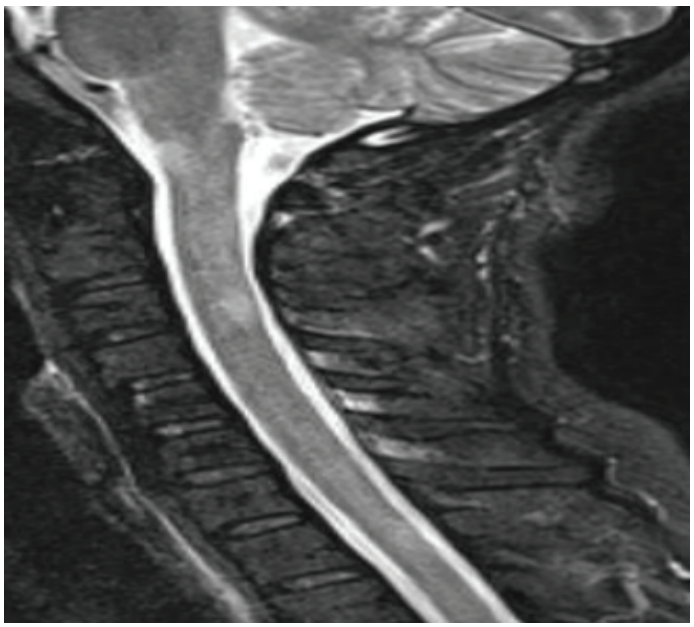

Figure 3. Demyelinating plaques on servical magnetic resonance imaging. Sagittal section image with T2 FLAIR

It was detected a slowing in the speed of visual evoked potential for right eye (123 ms) although there were normal both brainstem auditory evoked potential and sensory evoked potential. NMO antibody was negative. Furthermore, oligoclonal IgG bands was demonstrated in cerebrospinal fluid by obtain lumbar puncture (Index of IgG: 2.2). Based on the findings, MS was diagnosed and high dose methylprednisolone therapy (1 g/day) for 7 days administered to the patient. Then, the case was referred to Endocrinology department because of she has high titers of thyroid autoantibodies. Laboratory revealed hypergonadotropic hypogonadism and hypovitaminosis b12. Furthermore, it was also detected positivity of antinuclear antibody (ANA) as well as both anti-thyroid peroxidase and anti-thyroglobulin antibodies.

Table 1. Biochemical and Hormonal Results of the Patient

Test	Result	Reference Range
Glucose	86 mg/dL	70 – 100
Urea	23 mg/dL	15 – 40
Creatinine	0.66 mg/dL	0.5 – 0.9
AST	22 IU/L	< 40
ALT	24 IU/L	< 55
Total Protein	6.7 g/dL	6.0 – 8.3
Albumine	4.0 g/dL	3.5 – 5.0
Total Cholesterol	192 mg/dL	90 – 200
LDL Cholesterol	90 mg/dL	< 100
HDL Cholesterol	82 mg/dL	> 50
Triglyceride	100 mg/dL	< 150
Sodium	140 mmol/L	136 – 145
Potassium	3.98 mmol/L	3.5 – 5.1
Calcium	9.1 mg/dL	8.4 – 10.2
Parathyroid Hormone	43.96 pg/mL	15 – 68.3
25-OH cholecalciferol	50 ng/mL	25 – 80
FSH	99.5 mIU/mL	23 – 116 *
LH	40 mIU/mL	16 – 54 *
Estradiol	<5 pg/mL	< 40 *
Prolactin	12.69 ng/mL	5.18 – 25.53 **
TSH	2.51 µIU/mL	0.27 – 4.5
Free T3	3.21 pg/mL	2 – 4.4
Free T4	0.95 ng/dL	0.93 – 1.71
Cortisol	18 µg/dL	4.6 – 22.8
Vitamin B12	165 pg/mL	230 – 900

AST: Aspartate Aminotransferase
ALT: Alanine Aminotransferase
LDL: Low Density Lipoprotein
HDL: High Density Lipoprotein
FSH: Follicle Stimulating Hormone
LH: Luteinizing Hormone
TSH: Thyroid Stimulating Hormone
T3: Triiodothyronine
T4: Thyroxine
* in postmenopausal women
** in nonpregnant women

The patient was euthyroid status in the first hormonal evaluation despite the presence of thyroid autoantibodies. On neck ultrasonography, the thyroid gland was heterogeneous and hypoechoic a finding consistent with chronic thyroiditis. The clinical picture was considered to be an APS due to the coexistence of autoimmune thyroiditis and early menopause. Likewise, the presence of MS has also supported the possibility of an autoimmune condition. Thereupon, we performed a comprehensive investigation including hormonal, biochemical, immunological, and serological tests. The laboratory findings are summarized in Table 1 and Table 2.

Table 2. Serological and Immunological Results of the Patient

Test	Result	Reference Range
ESR	12 mm/h	< 20
CRP	2.66 mg/L	< 5
RF	0.2 IU/mL	< 14
C3	1.03 g/L	0.9 – 1.8
C4	0.35 g/L	0.1 – 0.4
ANA (IFA)	Positive (homogenous)	–
Anti ds-DNA (IgG)	Negative	–
Anti Cardiolipin (IgM)	<3 U/mL	< 12
Anti Cardiolipin (IgG)	<3 U/mL	< 12
Anti Phospholipid (IgM)	Negative	< 12
Anti Phospholipid (IgG)	Negative	< 12
Anti TPO	1077 IU/mL	< 35
Anti TG	410 IU/mL	< 20
Anti SS-A	Negative	< 12
Anti SS-B	Negative	< 12
Anti Scl 70	Negative	–
Anti RNP	Negative	–
Anti Centromer	Negative	–
Anti Histone	Negative	< 40
Borrelia Burgdorferi* (IgM)	Negative	< 9
Borrelia Burgdorferi* (IgG)	Negative	< 9
c-ANCA	15.7 U/mL	< 18
p-ANCA	<3 U/mL	< 18

ESR: Erytrhocyte Sedimentation Rate
CRP: C-reactive protein
RF: Rheumatoid Factor
C3: Complement 3
C4: Complement 4
IFA: Immunofluorescence Assay
ANA: Anti nuclear antibody
ds-DNA: double-stranded DNA
Ig: Immunoglobulin
TPO: Thyroid peroxidase
TG: Thyroglobulin
SS: Sjogren's Syndrome
Scl: Scleroderma
RNP: Ribonucleoprotein
* for Lyme disease
c-ANCA: cytoplasmic Antineutrophil cytoplasmic antibody
p-ANCA: perinuclear Antineutrophil cytoplasmic antibody

Based on these results, the patient with MS who has chronic autoimmune thyroiditis and primary ovarian failure was diagnosed with APS III. Despite ANA positivity, the findings were not enough to definitive diagnose Systemic Lupus Erythematosus according to "2015 ACR/SLICC Revised Criteria for Diagnosis of Systemic Lupus Erythematosus" (7). There were also not any remarkable results on complete blood counter, urine analysis and chest

x-ray of the patient. After all this, hormone replacement therapy was recommended to the patient both to relieve the symptoms related hypoestrogenemia and to keep from osteoporosis but this treatment was refused by the patient. Teriflunomide (14 mg/day) was started 3 months after the methylprednisolone therapy due to same symptoms was relapsed. Teriflunomide provided remission for MS, however overt hypothyroidism occurred in the course of the treatment. Therefore, levothyroxine (50 microgram per day) was added on to the treatment. The increase in serum level of thyroid stimulating hormone (TSH) after treatment with teriflunomide was shown in Table 3.

Table 3. Changes in Hormone Levels During Therapy with Teriflunomide

Test	Before treatment	3rd month of treatment	6th month of treatment
TSH	2.51 µIU/mL	4.24 µIU/mL	9.69 µIU/mL
Free T3	3.21 pg/mL	3.06 pg/mL	2.23 pg/mL
Free T4	0.95 ng/dL	0.93 ng/dL	0.78 ng/dL

The reference ranges of hormones have been shown on Table 1

DISCUSSION

Premature ovarian failure is the cessation of menses for more than 1 year before 40 years of age secondary to loss of ovarian function (8). However, autoimmunity against the ovaries could not been proven in our case despite the presence of thyroid autoantibodies. As a matter of fact that, no reliable ovary-specific tests exist for the diagnosis of autoimmune ovarian failure. While there is no direct test for autoimmune oophoritis, it can be suspected based on the presence of other autoimmune disorders, as evidenced by positive thyroid or adrenal antibodies (9). On the other hand, she had not any findings suggesting primary adrenal insufficiency such as hypotension, hypoglycemia, electrolyte imbalance, and darkness of skin color. The possibility of APS-II was excluded because of basal cortisol level has been found normal. The coexistence of autoimmune thyroiditis, hypovitaminosis b12 and primary ovarian failure has also strongly supported APS-III in our case.

Although APS's are associated with numerous both organ-specific and non organ-specific autoimmune diseases, only a few APS cases coexisting MS have been reported (10-13). In addition, it is known that immunomodulatory drugs including interferon β and alemtuzumab which are used for treatment of MS may lead to secondary autoimmune diseases, especially thyroid dysfunction. In a recent study, Flores and colleagues (14) have reported development of hypothyroidism in a case with MS who is treated with fingolimod that is a functional antagonist of sphingosine-1-phosphate receptors in lymphocytes. However, we could not find any case with MS who has occurred hypothyroidism during teriflunomide therapy in English literature up to the present. It is also difficult to prove exactly whether hypothyroidism is due to teriflunomide in our case because she had an autoimmune background such as primary ovarian failure and positivity of thyroid autoantibodies before the treatment of teriflunomide. It may be merely a coincidence in the basis of autoimmunity but we have considered that gradually risen overt hypothyroidism after inception of teriflunomide therapy is remarkable.

The alterations in the serum concentrations of thyrotropin and free thyroxine in the women with hypothyroidism sometimes results from estrogen-induced increases in the serum thyroxine-binding globulin concentration. This increase in binding would be expected to slow the entry of thyroxine into cells, including pituitary cells, thereby reducing thyroid hormone action in tissue (15). The increase of thyrotropin level in our patient could be explained if she had agreed to receive hormone replacement therapy for premature ovarian failure, whereas the suggested treatment had been rejected by the patient as mentioned above.

CONCLUSION

Consequently, the coexistence of APS and MS is a rare clinical entity. Moreover, hypothyroidism has been detected during teriflunomide therapy in the patient. Hypothyroidism was most likely a component of APS-III in our case, but it may also have been triggered by teriflunomide. Thus, we herein present this case. Despite all this, it is clear that much more observations is necessary about possible connection between teriflunomide therapy and thyroid dysfunction. Further knowledge of the metabolic and molecular mechanisms concerning with the interaction between MS and other autoimmune disorders may contributes to development new therapeutic strategies.

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REFERENCES

1. Neufeld M, Blizzard RM. Polyglandular autoimmune disease. In: Pinchera A, Doniach D, Fenzi DF, Baschieri L, eds. Autoimmune aspects of endocrine disorders. London, UK: Academic Press 1980;357-365.
2. Kasznicki J, Drzewoski J. A case of autoimmune urticaria accompanying autoimmune polyglandular syndrome type III associated with Hashimoto's disease, type 1 diabetes mellitus, and vitiligo. Endokrynol Pol 2014;65:320-3.

3. Popescu BF, Lucchinetti CF. Pathology of demyelinating diseases. Ann Rev Pathol 2012;7:185-217.
4. Maddison P, Kiely P, Kirkham B, et al. Leflunomide in rheumatoid arthritis: recommendations through a process of consensus. Rheumatology (Oxford) 2005;44:280-6.
5. Bruneau JM, Yea CM, Spinella-Jaegle S, et al. Purification of human dihydro-orotate dehydrogenase and its inhibition by A77 1726, the active metabolite of leflunomide. Biochem J 1998;336:299-303.
6. Xu X, Blinder L, Shen J, et al. In vivo mechanism by which leflunomide controls lymphoproliferative and autoimmune disease in MRL/MpJ-lpr/lpr mice. J Immunol. 1997;159:167-74.
7. Iraj Salehi-Abari. ACR/SLICC Revised Criteria for Diagnosis of Systemic Lupus Erythematosus. Autoimmune Dis Ther Approaches 2015;2:114.
8. North American Menopause Society. Early menopause guidebook. 6th edition. Cleveland, OH: North American Menopause Society 2006.
9. Kalu E, Panay N. Spontaneous premature ovarian failure: management challenges. Gynecol Endocrinol. 2008;24:273-9.
10. Boz C, Velioglu S, Altunayoglu V, et al. Central nervous system involvement in autoimmune polyglandular syndrome. Clinical Neurology and Neurosurgery 2003; 105:102-4.
11. Edwards LJ, Constantinescu CS. A prospective study of conditions associated with multiple sclerosis in a cohort of 658 consecutive outpatients attending a multiple sclerosis clinic. Mult Scler 2004;10:575-81.
12. Yokote H, Nagasawa M, Ichijo M, et al. Autoimmune polyendocrine syndrome-3 in a patient with late-onset multiple sclerosis. Neurologist. 2012;18:83-4.
13. Masuda S, Mori M, Hamada S, et al. Autoimmune polyendocrine syndrome type 3 in a multiple sclerosis patient. Clinical and Experimental Neuroimmunology 2015;6:299-303.
14. Flores J, Rito Y, Torres G, et al. Hypothyroidism in multiple sclerosis patient during fingolimod treatment. J Neurol Sci 2015;348:272-3.
15. Arafah BM. Increased need for thyroxine in women with hypothyroidism during estrogen therapy. N Engl J Med 2001;344:1743-9.