Reminder of important clinical lesson

A Filipino woman with autoimmune polyglandular syndrome

Cristina Vianzon Jaring, Maria Luisa Cecilia Rivera-Arkoncel, Frances Lina Lantion-Ang

Section of Endocrinology, Diabetes and Metabolism, Department of Medicine, University of the Philippines – Philippine General Hospital, Manila, Philippines

Correspondence to Dr Cristina Vianzon Jaring, cvjaring@gmail.com**Summary**

A 47-year-old Filipino woman presented with goitre of 3 months' duration. She had no symptoms of thyrotoxicosis or hypothyroidism. Her thyroid was diffusely enlarged. Thyrotropin was elevated and free thyroxine was low. Ultrasound revealed slightly enlarged thyroid with diffuse parenchymal disease. Antithyroid peroxidase antibody was elevated. She was started on levothyroxine at 1.6 mcg/kg body weight/day and dose was adjusted to maintain the thyrotropin level within normal limits. Four years after the diagnosis of Hashimoto's thyroiditis was made, the patient started to experience malaise, generalised weakness and fatigue. Functional screening for other autoimmune endocrinopathy was done. Fasting 8 a.m serum cortisol was noted to be markedly decreased. She was diagnosed with autoimmune polyglandular syndrome type 2 (Schmidt syndrome). Physiologic dose of prednisone was started which afforded significant improvement in the patient's symptoms. The patient is on regular follow-up and clinically well.

BACKGROUND

Autoimmune polyglandular syndrome (APS) is a rare polyendocrinopathy characterised by the failure of several endocrine glands as well as non-endocrine organs that is caused by an immune-mediated destruction of tissues.¹ An important responsibility for clinicians managing patients with endocrine gland deficiencies is to consider whether an individual with a single endocrine autoimmunity is at risk for the occurrence of a polyglandular disorder.² Treatment of organ insufficiency is identical whether it occurs in isolation or as part of an APS. Replacement therapy remains the cornerstone but some caution should be observed. Regular and long-term follow-up is necessary.

CASE PRESENTATION

The patient is a 47-year-old Filipino woman who developed goitre 3 months prior to consult. It was not accompanied with palpitations, tremors, easy fatigability, weight change, heat or cold intolerance, weakness, diarrhoea or constipation and eye changes. The goitre was stable in size, not associated with pain, dysphagia, dyspnoea, or hoarseness of voice. The review of systems was unremarkable.

She has no known medical illness. She has regular menstrual cycle and is a gravida 4 para 4. There is no family history of goitre, thyroid cancer, or autoimmune disorder. The patient has no vices.

Physical examination showed stable vital signs. She had diffusely enlarged thyroid gland measuring 4×2 cm (right lobe) and 5×3 cm (left lobe) with firm consistency. There were no eye signs. She had normal cardiac rate and rhythm, normal reflexes and no fine finger tremors. The rest of the physical examination was unremarkable.

INVESTIGATIONS

Thyroid function test showed elevated thyrotropin level at 95.9 mIU/l (N.V. 0.3–3.8) with low free thyroxine level at 6.4 pmol/l (N.V. 11–24). Thyroid ultrasound revealed

slightly enlarged thyroid gland with the following dimensions: 5.4×1.9×1.6 cm (right lobe) and 4.9×1.9×1.6 cm (left lobe); with note of diffuse parenchymal disease. Antithyroid peroxidase antibody level was noted to be elevated at 180.9 U/l (N.V. <100).

DIFFERENTIAL DIAGNOSIS

Initial assessment was Hashimoto's thyroiditis (International Classification of Diseases 10 code E06.3).

TREATMENT

The patient was started on levothyroxine replacement therapy at 1.6 mcg/kg body weight/day and regular follow-up was done. Levothyroxine dose was adjusted to maintain the thyrotropin level within normal limits.

Four years after the diagnosis of Hashimoto's thyroiditis was made, the patient started to experience malaise, generalised weakness and fatigue. On examination, she was noted to have normal blood pressure with no postural hypotension. The rest of the physical findings were unremarkable. During that time, repeat thyrotropin level was noted to be slightly elevated at 7.0 mIU/l (N.V. 0.3–3.8). The dose of levothyroxine was increased. Due to the appearance of the non-specific symptoms with just a relatively mild elevation in the thyrotropin level that could not fully account for the patient's manifestations and with the background of an autoimmune disorder, functional screening for other autoimmune endocrinopathy was done (table 1). Complete blood count was within acceptable levels. Fasting blood sugar was also within normal. Fasting 8 a.m serum cortisol was markedly decreased at 16.4 nmol/l (N.V. 138–690). She was then started on physiologic dose of prednisone. At this time, the patient was classified as having autoimmune polyglandular syndrome type 2, or Schmidt syndrome, because of the presence of adrenal insufficiency probably Addison's disease and Hashimoto's thyroiditis.

Table 1 Results of diagnostic tests done for the consideration of autoimmune polyglandular syndrome

	Result	Reference range
Functional test		
Thyroid stimulating hormone	95.9 mIU/l	0.3–3.8
Free T4	6.4 pmol/l	11.0–24.0
Fasting 8 a.m cortisol	16.4 nmol/l	138–690
Fasting blood sugar	3.97 mmol/l	3.9–6.1
Na	142.7 mmol/l	136–145
K	3.5 mmol/l	3.5–5.1
Ca	2.34 mmol/l	2.12–2.52
Haemoglobin	122 g/l	120–150
Serologic test		
Antithyroid peroxidase antibody	180.9 U/l	<100

OUTCOME AND FOLLOW-UP

On follow-up, there was significant improvement in the patient's symptom. Serum sodium, potassium and calcium were within acceptable levels. Peripheral blood smear did not show macrocytes or hypersegmented neutrophils. She was maintained on levothyroxine 2.7 mcg/kg body weight/day and prednisone 5 mg daily. Currently, she is clinically well and is on regular follow-up. She was advised on the possibility of occurrence of other autoimmune diseases and their manifestations. Her relatives were also advised of the possibility of the same condition.

DISCUSSION

Hashimoto's thyroiditis, also known as chronic lymphocytic thyroiditis, chronic autoimmune thyroiditis and lymphadenoid goitre, is an autoimmune thyroid disease characterised by the presence of autoantibodies, especially thyroid peroxidase antibodies, and intrathyroidal lymphocytic infiltration. It is the most common cause of hypothyroidism in iodine-sufficient areas and is basically treated with administration of levothyroxine sodium.

It is an observation that autoimmune disorders tend to co-exist in the same subjects and to cluster in families. Boelaert *et al*⁶ noted that the frequency of occurrence of another autoimmune disorder in patients with autoimmune thyroid disease was 9.67% in Graves' disease and 14.3% in Hashimoto's thyroiditis. Relative risks of other autoimmune diseases in Graves' disease or Hashimoto's thyroiditis were significantly increased (>10 for pernicious anaemia, systemic lupus erythematosus, Addison's disease, celiac disease and vitiligo). This study demonstrated that patients with a primary diagnosis of autoimmune thyroid disease are at significantly increased risk of additional autoimmune diseases.

APS, also known as polyglandular autoimmune syndrome, is a rare polyendocrinopathy characterised by the failure of several endocrine glands as well as non-endocrine organs that is caused by an immune-mediated destruction of tissues.¹ This usually leads to a hypofunctional state.⁴ APS type 1, also known as autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy, occurs in childhood with 1:1 female to male ratio. It is a rare condition (3/million) caused by mutations in the autoimmune regulator (AIRE) gene with an autosomal recessive pattern of inheritance. The main manifestations include mucocutaneous candidiasis, hypoparathyroidism and Addison's disease. Autoimmune polyglandular syndrome type 2 occurs in

adults between 16 and 40 years and has a female predilection. It is more common (1 in 15 000) than APS type 1 but is genetically complex and has no clear pattern of inheritance.⁵ APS type 2 is defined by the presence of two or more of the following: Addison's disease, autoimmune thyroid disease, type 1 diabetes mellitus. The occurrence of Addison's disease and autoimmune thyroid disease in a patient classifies him as having the Schmidt syndrome whereas those with Addison's disease and type 1 diabetes are labelled as having the Carpenter syndrome.¹ The patient is a 47-year-old female with no family history of autoimmune disease who was initially diagnosed with Hashimoto's thyroiditis and later developed adrenal insufficiency. Thus is the diagnosis of APS type 2, specifically Schmidt syndrome.

Another system of classification was used in the article by Betterle *et al*⁶ published in Clinical and Experimental Immunology in 2004. APS type 1 is defined by the presence of at least two of the following: chronic candidiasis, chronic hypoparathyroidism, Addison's disease. The occurrence of Addison's disease (always present) and autoimmune thyroid disease and/or type 1 diabetes in one patient classifies him under APS type 2. APS type 3 is the association of autoimmune thyroid disease with other autoimmune diseases, excluding Addison's disease and/or hypoparathyroidism. APS type 4 is the combination of organ-specific autoimmune diseases not included in the previous groups. Betterle further characterised the prevalence of disease combinations in APS type 2. The most common was the combination of Addison's disease and chronic thyroiditis, which occurred in more than half of cases (56.1%). This was the combination present in the patient. The prevalence of other combinations was as follows: Addison's and Graves' disease – 21.2%; Addison's disease and type 1 diabetes – 10.9%; Addison's disease, chronic thyroiditis, and type 1 diabetes – 9.6%; Addison's disease, Graves' disease and type 1 diabetes – 2.0%.

The pathogenesis of autoaggression in endocrine autoimmunity is considered multifactorial.¹ Upon exposure of a genetically-susceptible individual to an environmental trigger, an antigen-specific autoimmune response is initiated by antigen-presenting cells such as the dendritic cells. They pick up antigen molecules, fragment them, and present these fragments that activates antigen-specific T helper cells that stimulate the cellular immune response via cytotoxic T lymphocytes (T helper 1 or Th1 response) and/or the humoral immune response via the B lymphocytes (Th2 response). In the preclinical phase of the disease, production of organ-specific autoantibodies causes progressive immune-mediated destruction of endocrine tissues. Major organ destruction eventually causes secretory insufficiency (clinical phase).

Based on the pathophysiology, the clinical presentation of APS component diseases is often preceded by an asymptomatic latent period of months or years characterised by the presence of circulating disease-associated antibodies. Circulating organ- and cell-specific autoantibodies frequently detected in patients with the syndrome may be useful markers of future organ failure.⁴ The aforementioned concept may be seen in the stages in the development of Addison's disease. In the first stage, genetic predisposition is conferred through human leucocyte antigen (HLA) genes. In the second stage, events that

precipitate antiadrenal autoimmunity occur, although they are currently unknown. In the third stage, which involves presymptomatic disease, 21-hydroxylase autoantibodies predict future disease. Finally, in the fourth stage, overt Addison's disease develops.

Thus, after a variable period of latency, a proportion of patients may develop the other components of the syndrome, particularly those with evidence of subclinical disease such as an elevated thyroid stimulating hormone (TSH) or impaired glucose tolerance.¹⁻⁶ Clues to the presence of autoimmune polyglandular syndrome are uncovered by a thorough history (patient symptoms, family history) and physical examination plus laboratory findings of organ-specific autoantibodies and hormone deficiencies. A high index of suspicion needs to be maintained whenever one organ-specific autoimmune disorder is diagnosed in order to prevent morbidity and mortality from the index disease as well as the associated diseases. Syndromes of multi-organ failure induced by autoimmunity occur in well-recognised patterns and can be detected at an asymptomatic stage by screening high-risk individuals for circulating autoantibodies. In patients with autoimmune thyroid diseases with no clinical adrenal failure, autoantibodies to the adrenal cortex are present in about 1% of the cases and the cumulative risk of developing clinical disease in positive cases is about 30%.⁶ About 30% of subjects with positive adrenal antibodies progress to adrenal failure over a 6-year period. Many patients with thyroid autoantibodies but normal TSH progress to clinical disease (about 5% yearly). The number of autoantibodies present in a given individual serves as a guide to diseases that may develop, as the risk for a given disease tends to increase as the number and quantity of autoantibodies targeting that tissue increases.⁷ Depending on the number of autoantibodies present for type 1 diabetes, up to 90% will go on to develop the clinical disease.⁸

An important responsibility for clinicians managing patients with endocrine gland deficiencies is to consider whether an individual with a single endocrine autoimmunity is at risk for the occurrence of a polyglandular disorder.² From the clinical point of view, hardly ever does the syndrome blow up simultaneously with two or three main autoimmune diseases in one individual, while it usually initiates with a single disease (type 1 diabetes, Graves' disease, Hashimoto's thyroiditis, or Addison's disease), and sometimes even with a minor disease (vitiligo, pernicious anaemia, premature ovarian failure, alopecia, chronic atrophic gastritis).⁶ Some authors actually recognise the incomplete forms of APS type 2 (autoimmune thyroid disease or type 1 diabetes and adrenal autoantibodies; Addison's disease and either thyroid and/or islet cell autoantibodies).⁵

It is not clear what distinguishes a patient with a single disorder from a patient with multiple additional autoimmune disorders. One factor may simply be time, since patients develop additional disorders with increasing age,⁹ although clinicians need to remain vigilant for the development of other autoimmune conditions, regardless of the age of the patient.

Dittmar and Kahaly¹ noted the time interval (median) between manifestations of the first and second endocrinopathy. The longest time intervals were between type 1 diabetes and autoimmune thyroid disease (13 years) and

between vitiligo and autoimmune thyroid disease (16 years). The shortest time intervals, on the other hand, were between Addison's disease and type 1 diabetes (2 years) and between autoimmune thyroid disease and vitiligo (3 years). In general, when autoimmune thyroid disease was present as a first component disease, the time interval until the onset of another immunopathy was relatively short. For the patient, the time interval between the occurrence of her first endocrinopathy (Hashimoto's thyroiditis) and her second (Addison's disease) was 4 years.

When a rare disorder, such as autoimmune hypoparathyroidism, occurs spontaneously, the probability that other autoimmune disorders are present or will develop is high, and there is greater clinical utility in screening for other hormone deficiencies and/or for the presence of autoantibodies. When a common autoimmune disease is present in isolation, such as hypothyroidism, the development of additional autoimmune endocrine disorders is much less common, and further endocrine and serologic testing should be guided by clinical suspicion.⁷ Screening for other autoimmune endocrine disorders is mandatory especially if the patient presents with new or non-specific symptoms or if a patient remains unwell despite adequate treatment.

It is recommended by Betterle to screen patients with one organ-specific autoimmune disease for the circulating autoantibodies relevant to the other main diseases at the clinical diagnosis then every 2 or 3 years thereafter. However, as noted by Dittmar and Kahaly, not all patients show positive antibodies. And that, the absence of these antibodies does not exclude the disease. Therefore, they proposed a diagnostic approach to screen patients with APS which involves functional, serological and genetic screening. Functional screening confirms diagnosis and comprises determination of baseline hormone values (TSH, follicle stimulating hormone, luteinising hormone, free T4, testosterone, oestradiol, fasting morning cortisol and glucose), complete blood count and electrolytes (Na, K, Ca). On the other hand, detecting organ-specific autoantibodies by serologic screening verifies the aetiology of the disease and identifies patients who may develop autoimmune polyendocrinopathies. These include autoantibodies to islet cells, glutamic acid decarboxylase, IA2, thyroid peroxidase, thyroglobulin, TSH receptor, cytochrome P450 enzymes (21-OH, 17-OH, side chain cleavage), H-K-ATPase of the parietal cells, intrinsic factor, transglutaminase and gliadin. Genetic screening, according to the literature, is useful for APS 1 and less useful for type 2. Optional genetic screening tests include molecular analysis of AIRE gene, especially for APS 1, and HLA typing and subtyping. Dittmar and Kahaly then recommended that for patients with monoglandular autoimmune endocrinopathy, functional screening for APS should be done every 3 years until the age of 75. If pathological findings, such as the occurrence of a second autoimmune endocrine disease, are noted, measurement of organ-specific autoantibodies should be added. Furthermore, functional screening for autoimmune endocrine diseases of the first-degree relatives of these patients with newly-diagnosed APS may also be done. It was noted that approximately one in seven first-degree relatives of patients with APS have an unrecognised endocrine disorder, usually the relatively common autoimmune thyroiditis.¹⁰

The therapies regarding the different components of APS 2 are similar whether they occur as single or in multiple association with other autoimmune diseases, and the disorders should be treated as they are diagnosed. Hormone replacement therapy remains the cornerstone – glucocorticoids and mineralocorticoids for Addison's disease, levothyroxine for hypothyroidism and insulin for type 1 diabetes.

Some caution should be observed in the treatment of patients with APS type 2. It is worth remembering that thyroid hormone replacement therapy in patients with autoimmune hypothyroidism and misdiagnosed adrenal insufficiency can precipitate an adrenal failure because thyroid hormone increases the hepatic clearance of cortisol. Clinicians should maintain a high degree of alertness for underlying adrenal failure before initiating thyroid hormone replacement.⁵ On the other hand, deterioration of glycemic control with recurrent hypoglycemia and a decrease in total insulin requirements can be the presenting sign of Addison's disease in patients with type 1 diabetes. Therefore, before initiating therapy with thyroxine or modifying insulin dosage, it is prudent to investigate the possible coexistence of an underlying adrenal insufficiency.⁶

Mortality in patients with primary adrenal insufficiency is elevated approximately twofold compared with the background population, primarily as a consequence of unrecognised adrenal crisis.⁵ Early detection of Addison's disease can prevent mortality from a hypotensive crisis and spare individuals what is often years of disease prior to diagnosis. Uncontrolled thyroid hormone imbalances can be emergencies on rare occasions, especially in the older. Complications of type 1 diabetes, both acute and chronic, are as important in the APS setting as in isolated pancreatic disease.² Quality of life is often impaired, mainly due to unpredictable fatigue, lack of energy, depression and anxiety.⁵

In view of the possibly long-time interval between the manifestation of the first and further autoimmune endocrinopathies, regular and long-term observation of patients with endocrine autoimmune disorder is necessary. Patient's education about possible co-existing disease is important and they should be advised of the symptoms of the disorders for which they are at high-risk. Relatives of patients should also be advised of the possibility of the same condition.

Learning points

- ▶ High index of suspicion for autoimmune polyglandular syndrome needs to be maintained whenever one organ-specific autoimmune disorder is diagnosed in order to prevent morbidity and mortality from the index disease as well as the associated diseases.
- ▶ The key to successfully manage patients with APS is to identify and treat their autoimmunities before they cause significant morbidity and mortality.
- ▶ Treatment of organ insufficiency is identical whether it occurs in isolation or as part of an APS. Replacement therapy remains the cornerstone but some caution should be observed.
- ▶ Regular and long-term follow-up is necessary in the management of patients with endocrine autoimmune disorders. First-degree relatives of patients with APS should also be regularly screened.

Competing interests None.

Patient consent Obtained.

REFERENCES

1. Dittmar M, Kahaly GJ. Polyglandular autoimmune syndromes: immunogenetics and long-term follow-up. *J Clin Endocrinol Metab* 2003;**88**:2983–92.
2. Jameson J, De Groot L. *Endocrinology, Adult and Pediatric*. Sixth edition. Philadelphia, PA: Saunders 2010.
3. Boelaert K, Newby PR, Simmonds MJ, et al. Prevalence and relative risk of other autoimmune diseases in subjects with autoimmune thyroid disease. *Am J Med* 2010;**123**:183.e1–9.
4. Meyerson J, Lechuga-Gomez EE, Bigazzi PE, et al. Polyglandular autoimmune syndrome: current concepts. *CMAJ* 1988;**138**:605–12.
5. Owen CJ, Cheetham TD. Diagnosis and management of polyendocrinopathy syndromes. *Endocrinol Metab Clin North Am* 2009;**38**:419–36.
6. Betterle C, Lazzarotto F, Presotto F. Autoimmune polyglandular syndrome type 2: tip of an iceberg? *Clin Exp Immunol* 2004;**137**:225–33.
7. Henderson K, Baranski T, Bickel P, et al. *Endocrinology Subspecialty Consult*. Second edition. Saint Louis, Missouri: Washington University School of Medicine 2009.
8. Michels AW, Eisenbarth GS. Autoimmune polyendocrine syndrome type 1 (APS-1) as a model for understanding autoimmune polyendocrine syndrome type 2 (APS-2). *J Intern Med* 2009;**265**:530–40.
9. Eisenbarth GS, Gottlieb PA. Autoimmune polyendocrine syndromes. *N Engl J Med* 2004;**350**:2068–79.
10. Kahaly G. Polyglandular autoimmune syndromes. *Eur J Endocrinol* 2009;**161**:11–20.

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