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Case Report

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A Significant Discrepancy Between Endocrinological and Clinical Phenotype and Immunological Phenotype in Autoimmune Polyglandular Syndrome Type 3

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Abstract

Autoimmune polyglandular syndrome (APS) is made up of a group of autoimmune disorders of the endocrine glands. In APS type 3, autoimmune thyroiditis occurs with another organ-specific autoimmune disease. APS type 3 is also associated with systemic autoimmune diseases such as sarcoidosis, Sjögren's syndrome and rheumatoid arthritis. We describe a 53-year-old woman with APS type 3 who showed a significant discrepancy between endocrinological and clinical phenotype and immunological phenotype.

Keywords: Autoimmune thyroiditis; Autoimmune polyglandular syndrome; Rheumatoid arthritis; Sjögren's syndrome; Type 1 diabetes

Introduction

In autoimmune polyglandular syndrome (APS) type 3, autoimmune thyroiditis occurs with another organ-specific autoimmune disease, but not with autoimmune adrenalitis [1]. Other systemic autoimmune diseases can include type 1 diabetes mellitus, Sjögren's syndrome, and rheumatoid arthritis. Here, we report a patient with APS type 3 who showed a significant discrepancy between endocrinological and clinical phenotype and immunological phenotype.

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Case Report

A 53-year-old woman was diagnosed as having autoimmune thyroiditis due to the swelling of thyroid and the positivity for anti-thyroid peroxidase antibody (anti-TPO ab) and anti-thyroglobulin antibody (anti-TG ab) 25 years ago, however, she did not require thyroxin substitution because her thyroid function test was normal. She was also diagnosed as having Sjögren's syndrome due to dryness of eye and mouth and the positivity for anti-SSA/Ro antibody (anti-SSA/Ro ab) and anti-SSB/La antibody (anti-SSB/La ab) 4 years ago, and she has been treated by cevimeline hydrochloride hydrate. She was referred to our hospital due to hyperglycemia. Her body weight was 62.9 kg and height 157.4 cm (BMI 25.4 kg/m^2). Plasma glucose (335 mg/dL) and HbA1c (8.8%) levels were significantly elevated. Although titers of anti-TPO ab and anti-TG ab were significantly high, serum levels of free triiodothyronine, free thyroxine and thyroid stimulating hormone were within normal range. The titers of both anti-glutamic acid decarboxylase antibody (anti-GAD ab) and anti-insulinoma-associated protein-2 antibody (anti-IA-2 ab) were remarkably high, however, the urinary C-peptide level was within normal range (Table 1), suggesting the preserved beta-cell function. Her blood glucose levels were 101 - 167 mg/dL by using 2 units of insulin glulisine before each meal. Her adrenal function was normal. Although she has been diagnosed as having APS type 3, she was euthyroid and insulin-independent. Further, titer of rheumatoid factor (RF) was remarkably high, however, she did not show arthritis and her serum anti-cyclic citrullinated peptide antibody (anti-CCP ab) and C-reactive protein (CRP) were negative (Table 1).

Discussion

APS is made up of a group of autoimmune disorders of the endocrine glands [2]. APS shows failure of the glands to produce their hormones. APS type 3, in contrast to APS type

Table 1. Clinical, Immunological, and Endocrinological Characteristics of Our Patient with Autoimmune Polyglandular Syndrome Type 3

Autoantibodies	Titer	Suspected diseases	Endocrinological findings	Symptoms and other data
anti-TPO ab	> 600 IU/ml (NR < 16)	Hashimoto's disease	TSH 3.62 μIU/mL (NR, 0.54 - 4.26) free T3 3.51 pg/mL (NR, 2.39 - 4.06) free T4 1.11 ng/dL (NR, 0.71 - 1.52)	asymptomatic
anti-TG ab	298 IU/mL (NR < 28)			
anti-GAD ab	10 000 U/Ml (NR < 1.5)	type 1 diabetes	urinary C-peptide 70 μg/day (NR, 29.2 - 167)	BS 335 mg/dL HbA1c 8.8%
anti-IA-2 ab	11.0 U/mL (NR < 0.4)			
anti-SSA/Ro ab	> 500 U/mL (NR < 10)	Sjögren's syndrome		dry eye and dry mouth
anti-SSB/La ab	139 U/Ml (NR < 10)			
RF	320 IU/mL (NR < 20)	rheumatoid arthritis		asymptomatic anti-CCP ab (-) CRP (-)

ab: antibody; BS: blood sugar; CCP: cyclic citrullinated peptide; CRP: C-reactive protein; GAD: glutamic acid decarboxylase; IA-2: insulinoma-associated protein-2; NR: normal range; RF: rheumatoid arthritis; T3: triiodothyronine; T4: thyroxine; TG: thyroglobulin; TPO: thyroid peroxidase; TSH: thyroid stimulating hormone.

Table 2. Major Component Diseases and Minor Autoimmune Diseases in Each Type of Autoimmune Polyglandular Syndrome [1]

	Type 1	Type 2	Type 3	Type 4
major component diseases	Addison disease	Addison disease	thyroid autoimmune diseases	Addison disease
	hypoparathyroidism	thyroid autoimmune diseases	3A-type 1 diabetes	
	candidiasis	type 1 diabetes	3B-pernicious anemia	
			3C-vitiligo, alopecia, other organ-specific autoimmune diseases	
minor autoimmune diseases	type 1 diabetes	myasthenia gravis	Celiac disease	gonadal failure
	gonadal failure	gonadal failure	malabsorption	malabsorption
	pernicious anemia	vitiligo	gonadal failure	hypophysitis
	malabsorption	alopecia	sarcoidosis	autoimmune hepatitis
	vitiligo	pernicious anemia	Sjögren's syndrome	pernicious anemia
	alopecia		rheumatoid arthritis	myasthenia gravis
			myasthenia gravis	vitiligo
				alopecia

1 and 2 [3], does not involve the adrenal dysfunction (Table 2) [1]. In APS type 3, autoimmune thyroiditis occurs with another organ-specific autoimmune disease (Table 2) [1]. APS type 3 can be further classified into the 3 subgroups. Autoimmune thyroiditis with type 1 diabetes mellitus which developed in my patient is categorized as APS type 3A. APS type 3 is associated with organ-specific autoimmune diseases such as Celiac disease and myasthenia gravis, and systemic autoimmune diseases such as sarcoidosis, Sjögren's syndrome and rheumatoid arthritis [1].

Most patients with APS type 3 show abnormal thyroid function and decreased insulin secretion [4-6]. We experience a very rare APS type 3 middle-aged patient who showed normal thyroid and preserved beta-cell function in spite of the existence of remarkably high titer of autoantibodies (anti-TPO ab, anti-TG ab, anti-GAD ab and anti-IA-2 ab). Further, she presented with symptoms of Sjögren's syndrome (dryness of eye and mouth) and has been treated, showing the positivity for anti-SSA/Ro antibody and anti-SSB/La antibody. However, in spite of remarkably high titer of RF, she did not show arthritis and her serum anti-CCP ab and CRP were negative (Table 1).

APS is diverse, and its diversity is a characteristic that is both clinically important and very informative to understand its underlying basic immunological mechanisms and features [7-9]. An accumulation of similar cases to our patient may prompt us to understand the pathogenesis for APS.

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