Clinical Case Report

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Autoimmune polyglandular syndrome type III associated with antineutrophil cytoplasmic autoantibody-mediated crescentic glomerulonephritis

A case report and literature review

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Abstract

Rationale: Polyglandular autoimmune syndromes (PAS) are a heterogeneous group of rare diseases characterized by the association of at least 2 organ-specific autoimmune disorders, concerning both the endocrine and nonendocrine organs. Type III is defined as the combination of autoimmune thyroid disease and other autoimmune conditions (other than Addison disease), and is divided into 4 subtypes. We describe a patient with Hashimoto thyroiditis, adult-onset Still disease, alopecia, vasculitis, antineutrophil cytoplasmic antibody (ANCA)-mediated crescentic glomerulonephritis, and hyperparathyroidism. Co-occurrence of these 5 diseases allowed us to diagnose PAS type IIIc. The rare combination of these different diseases has not been reported before.

Patient concerns: A 51-year-old woman was admitted in April, 2019 after the complaint of an enlarged thyroid. She was diagnosed with Hashimoto thyroiditis at the age of 36. At age 40, she was diagnosed with an adult-onset Still disease. Three months before admission, she experienced renal insufficiency. After admission, she was diagnosed with hyperparathyroidism.

Diagnosis: Renal biopsy revealed renal vasculitis and crescentic nephritis. Antineutrophil cytoplasmic autoantibody showed that human perinuclear ANCA and myeloperoxidase ANCA were positive. Therefore, the patient was diagnosed with vasculitis and ANCA-mediated crescentic glomerulonephritis. After admission, parathyroid single-photon emission computed tomography/computed tomography fusion image demonstrated the presence of hyperparathyroidism.

Interventions: The patient was treated with high-dose methylprednisolone pulse therapy (0.1 g/d) for vasculitis and ANCA-mediated crescentic glomerulonephritis, calcium and vitamin D3 (600 mg/d elemental calcium [calcium carbonate] and 2.5 μg/d active vitamin D_3) for hyperparathyroidism, and levothyroxine sodium (50 ug/d) for Hashimoto thyroiditis.

Outcomes: Up to now, serum thyroid-stimulating hormone, total triiodothyronine, total thyroxine, free triiodothyronine, and free thyroxine were within the normal ranges. Patient's renal function did not deteriorate.

Lessons: We report a patient with Hashimoto thyroiditis, adult-onset Still disease, alopecia, vasculitis, ANCA-mediated crescentic glomerulonephritis, and hyperparathyroidism, which is a very rare combination. We present this case as evidence for the coexistence of several different immune-mediated diseases in the clinical context of a PAS IIIc.

Abbreviations: anti-Tg = antithyroglobulin, anti-TPO = antithyroid peroxidase, ANCA = antineutrophil cytoplasmic antibody, FT3 = free triiodothyronine, FT4 = free thyroxine, PAS = polyglandular autoimmune syndromes, TSH = thyroid-stimulating hormone, TT3 = total triiodothyronine, TT4 = total thyroxine.

Keywords: adult-onset Still disease, antineutrophil cytoplasmic autoantibody, autoimmune polyglandular syndromes, crescentic glomerulonephritis, Hashimoto disease

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S.T. and B.X. contributed equally to this work.

The authors have no conflicts of interest to disclose.

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1. Introduction

As the incidence of autoimmune disease has gradually increased over the past 10 years, polyglandular autoimmune syndromes (PAS) should be paid significant attention by physicians. PAS are a group of autoimmune disorders characterized by endocrine tissue destruction causing multiple gland malfunction. The classification of PAS proposed in 1980 by Neufeld and Blizzard[1] based on clinical features included 4 main types of PAS: type I, type II, type III, and type IV. In PAS III, autoimmune thyroiditis occurs together with another organ-specific autoimmune disease. PAS III can be further divided into 3 subtypes: PAS IIIa, autoimmune thyroiditis with immune-mediated diabetes mellitus; PAS IIIb, autoimmune thyroiditis with pernicious anaemia; and PAS IIIc, autoimmune thyroiditis with vitiligo, alopecia, and/or other organ-specific autoimmune disease.[2] In this article, we present a rare case of patient affected by PAS IIIc (Hashimoto disease accompanied with vasculitis, antineutrophil cytoplasmic antibody [ANCA]-mediated crescentic glomerulonephritis, adult-onset Still disease, and hyperparathyroidism).

2. Case report

A 51-year-old woman was admitted in April, 2019 after the complaint of an enlarged thyroid. Fifteen years before admission, during her annual physical examination, her titers of antithyroid peroxidase (anti-TPO) and anti-thyroglobulin (anti-Tg) increased in the serum. Thyroid ultrasound revealed an enlarged thyroid gland with diffuse hypoechoic lesion. Her free thyroxine (FT4) slightly decreased, and her thyroid-stimulating hormone (TSH) increased. She was diagnosed with Hashimoto thyroiditis and treated with levothyroxine sodium (Na) (50 μg/d). After 3 years, she stopped taking levothyroxine Na. At age 40, she was diagnosed with adult-onset Still disease due to fever, rash, and arthralgia. She was treated with methylprednisolone for 18 days, and her condition sufficiently improved. Hence, she was discharged from the hospital.

Three months before admission, she experienced alopecia and renal insufficiency (creatinine 265 μmol/L; glomerular filtration rate 22.03 mL/min). Considering her renal insufficiency, renal biopsy was performed. Light microscopy revealed renal vasculitis and crescentic nephritis (Fig. 1A). Serum antinuclear antibodies were positive (1:100). Antineutrophil cytoplasmic autoantibody

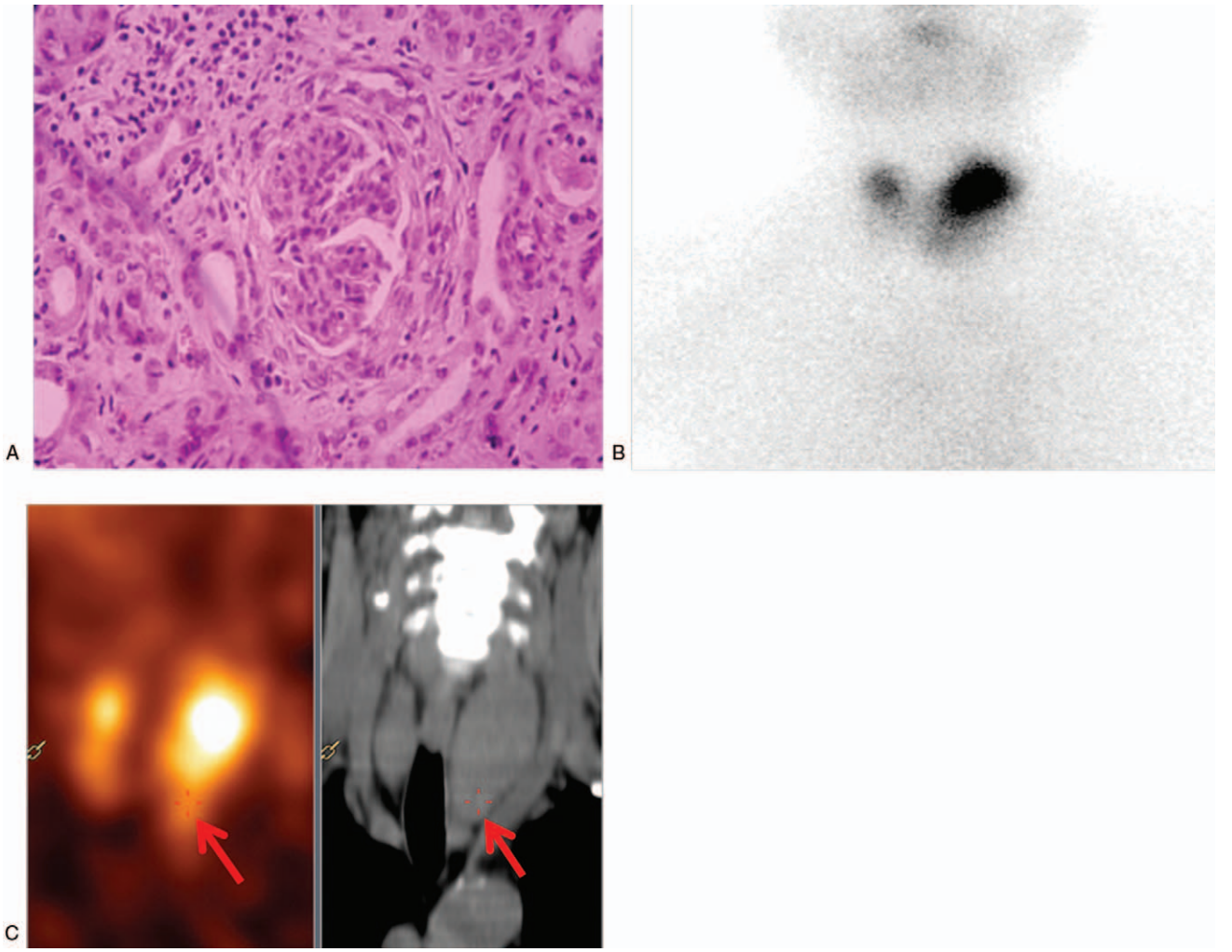

Figure 1. (A) Renal biopsy (hematoxylin and eosin staining ×200) showing the interstitial and perivascular infiltrate comprising lymphocytes and eosinophils, fibrinoid necrosis, and glomerular, parietal epithelial cell hyperplasia. (B) ^{99}Technetium scan revealing a high tracer uptake in the left upper thyroid. (C) Parathyroid single-photon emission computed tomography/computed tomography fusion image showing a slightly lower density below the left thyroid with a slightly higher concentration of radioactivity (as indicated by the red arrows).

showed that perinuclear ANCA and myeloperoxidase ANCA were positive. Therefore, vasculitis and ANCA-mediated crescentic glomerulonephritis were considered. The patient was treated with high-dose methylprednisolone pulse therapy (0.1 g/d).

Table 1

Laboratory data on admission.

Blood chemistry	
Fasting glucose	5.74 (normal, 3.9–6.1 mmol/L)
Urea nitrogen	**9.13** (normal, 2.8–7.6 mmol/L)
Creatinine	**162.65** (normal, 48–100 μmol/L)
Na	137.6 (normal, 136–145 mmol/L)
K	4.42 (normal, 3.5–5.2 mmol/L)
Ca	2.16 (normal, 2.1–2.65 mmol/L)
P	1.44 (normal, 0.81–1.45 mmol/L)
Aspartate transaminase	15.75 (normal, 8–40 IU/L)
Alanine aminotransferase	9.41 (normal, 5–40 IU/L)
Albumin	39.99 (normal, 35–52 g/L)
Lactate dehydrogenase	184.02 (normal, 80–248 IU/L)
γ-glutamyl transferase	42.41 (normal, 8–57 IU/L)
Alkaline phosphatase	52.24 (normal, 30–120 IU/L)
Total bilirubin	8.7 (normal, 5–21 umol/L)
Ferritin	**173.5** (normal, 5–130 ng/mL)
Folate	7.4 (normal, ≥3.2 ng/mL)
Vitamin B12	207.4 (normal, 180–916 pg/mL)
Hemoglobin	**86** (normal, 110–150 g/L)
Red blood cells	**3.24** (normal, 3.5–5 × 10^{12}/L)
White blood cells	7.46 (normal, 4–10 × 10^{9}/L)
Lymphocyte	2.81 (normal, 0.8–4 × 10^{9}/L)
Platelets	**477** (normal, 100–300 × 10^{9}/L)
Mean corpuscular volume	81.8 (normal, 80–100 fL)
Mean corpuscular hemoglobin	26.5 (normal, 27–34 pg)
Mean corpuscular hemoglobin concentration	325 (normal, 320–360 g/L)
Parathyroid hormone	**152.4** (normal, 15–65 pg/mL)
Urinalysis	
Protein	2+
Glucose	Negative
Blood	Negative
Ketone	Negative
Autoantibodies	
Anti-TPO	**600** (normal, 0–34 IU/ml)
Anti-Tg	**4000** (normal, 0–115 IU/ml)
Anti-TRAb	**40** (normal, 0.1–1.75 IU/L)
Islet cell antibody	Negative
Anti-SSA	Negative
Anti-SSB	Negative
Anti-SM/RNP	Negative
Antinuclear antibodies	**Positive (1:100)**
Anti-ASMA	Negative
Anti-SCL-70	Negative
Anti-ds DNA	Negative
Anti-mitochondrial antibodies	Negative
Anti-Jo-1	Negative
cANCA	Negative
pANCA	**Positive**
MPO-ANCA	**Positive**
Rheumatic factor	<20 (normal, <20 IU/mL)
Immunoglobulin G	**23.2** (normal, 8–16 g/L)
Immunoglobulin M	**3.1** (normal, 0.5–2.2 g/L)

Abnormal values are indicated in bold.

Anti-ASMA = antismooth muscle antibodies, anti-ds DNA = double-stranded DNA antibody, anti-Jo-1 = antibody against histidyl-tRNA synthetase, Anti-SCL-70 = anti-DNA topoisomerase I, anti-SM/RNP = antibodies against the Smith antigen/ribonucleoprotein, anti-SSA = antibodies against Sjogren syndrome antigen A, anti-SSB = antibody against Sjogren syndrome antigen B, anti-Tg = antithyroglobulin, anti-TPO = antithyroid peroxidase, anti-TRAb = antihyroid-stimulating hormone receptor, cANCA = human antineutrophil cytoplasmic antibody, MPO-ANCA = myeloperoxidase antineutrophil cytoplasmic antibody, pANCA = human perinuclear antineutrophil cytoplasmic antibody.

Upon admission, her body mass index was 21 kg/m^2, temperature 37.1°C, blood pressure 160/90 mm Hg, and pulse rate 90/min (regular). On physical examination, she presented with diffusely enlarged thyroid. There was slight exophthalmos. Laboratory data on admission were as follows (Table 1): urinalysis showed positive protein (2+), but no glucose, ketonuria, and blood. Blood analysis revealed mild anemia (hemoglobin 86 g/dL). Patient's renal function did not deteriorate. Fasting glucose, serum lipids, and electrolytes were within the normal ranges. The circadian rhythms of serum adrenocorticotropic hormone, cortisol, and renin were normal. Computed tomography scan of the adrenal glands and magnetic resonance imaging scan of the pituitary gland were normal. According to hormone analyses (2019-2-28), serum free triiodothyronine (FT3) (10.76 pmol/L) and FT4 (30.3 pmol/L) levels increased with a suppressed TSH level (0.005 mIU/mL) in the serum. Immunoglobulin G (23.2 g/L) and immunoglobulin M (3.1 g/L) increased. The titers of anti-TPO (600 IU/mL), anti-Tg (4000 IU/mL), and antithyrotropin receptor antibodies (40I U/L) increased. Thyroid ultrasound image showed diffusely enlarged thyroid gland without nodules, confirming the diagnosis of thyrotoxicosis. The radioactive iodine-131 uptake rate showed the following: 2 hours (radioactive iodine uptake rate, 7.16% [reference range 5%–15%]), 4 hours (radioactive iodine uptake rate, 11.34% [reference range 10%–20%]), and 24 hours (radioactive iodine uptake rate, 21.94% [reference range 20%–35%]). We suspected that it was a transient thyrotoxicosis, and the antithyroid therapy (methimazole) was not adapted. The results of thyroid hormone follow-up are shown in Table 2. Additionally, the serum parathyroid hormone (152.4 pg/mL) significantly increased. ^{99}Technetium scan demonstrated a high tracer uptake in the left upper thyroid (Fig. 1B), which was associated with thyroid hyperplasia. Parathyroid single-photon emission computed tomography/computed tomography fusion image showed a slightly lower density below the left thyroid with a slightly higher concentration of radioactivity (Fig. 1C). Regarding bone mineral density, an osteoporosis was defined by dual-energy x-ray absorptiometry (the T score of the patient was −3.17 standard deviation [SD] in the lumbar vertebra and −2.63 SD in the right articulatio coxae, lower than the reference value, which was −2.5 SD). Therefore, the patient was diagnosed with hyperparathyroidism and was treated with calcium and vitamin D3 (600 mg/d elemental calcium [calcium carbonate] and 2.5 μg/d active vitamin D3).

Table 2

The results of thyroid hormone follow-up.

Hormone analyses	First test (2019–2-28)	Second test (2019-3-15)	Third test (2019-4-15)	Last test (2019-5-16)
TSH (normal, 0.372–4.94 mIU/L)	0.005	0.284	5.08	4.82
TT3 (normal, 1.35–3.15 nmol/L)	None	1.29	1.19	2.88
TT4 (normal, 70–156 nmol/L)	None	46.5	38	78
FT3 (normal, 3.1–6.8 pmol/L)	10.76	2.49	2.28	3.56
FT4 (normal, 12–22 pmol/L)	30.3	6.4	5.6	13

FT3 = free triiodothyronine, FT4 = free thyroxine, TSH = thyroid-stimulating hormone, TT3 = total triiodothyronine, TT4 = total thyroxine.

This study was conducted in accordance with the recommendations of the Ethics Committee of the China-Japan Union Hospital of Jilin University, and all the participants provided written informed consent for the publication of this case report.

3. Discussion

Considering the subtle manifestations of Hashimoto thyroiditis and its insufficient clinical features, the early detection of this disease is significantly hard. Hashimoto thyroiditis has a variety of clinical manifestations, which can be characterized by hyperthyroidism, hypothyroidism, and a normal gland. In our case, hormone analyses on admission (2019-2-28) showed increased circulating FT3 (10.76 pmol/L) and FT4 (30.3 pmol/L) with a decreased TSH level (0.005 mIU/mL) in the serum. Hormone analysis after hospital discharge showed that TSH level gradually increased, and FT3, FT4, total triiodothyronine (TT3), and total thyroxine (TT4) gradually decreased. The third hormone analysis (2019-4-15) showed the low level of circulating TT3 and FT3 (TT3, 1.19 nmol/L; FT3, 2.28 pmol/L) and TT4 (TT4, 38 nmol/L; FT4, 5.6 pmol/L) with an increased TSH level (5.08 mIU/mL) in the serum. This was due to the release of thyroxine after thyroid follicle damage, rather than increased thyroxine synthesis; thyroxine levels will decrease over time. Subsequently, hyperthyroidism disappeared and even transitioned into hypothyroidism. In our case, the patient was finally diagnosed with hypothyroidism and received levothyroxine Na (50 μg/d). The last hormone analysis (2019-5-16) showed that the sera TSH, TT3, TT4, FT3, and FT4 were within the normal ranges. In the case of the presented patient, chronic kidney disease was due to hyperparathyroidism. Patients with chronic kidney disease are at risk of calcium and phosphorus metabolism disorders and osteoporosis. The parathyroid gland was stimulated by hypocalcemia and hyperphosphatemia for a long time, and it was easy to secrete a large amount of parathyroid hormone; subsequently, parathyroid hyperplasia was observed.

Polyglandular autoimmune syndrome is defined as multiple endocrine endorgan failure presenting over a variable period of time. Patients with PAS have an increased incidence of autoimmune diseases affecting both the endocrine and non-endocrine organs. The latter disorders include alopecia, vitiligo, pernicious anemia, Addison disease, insulin-dependent type 1 diabetes, rheumatoid arthritis, myasthenia gravis, chronic active hepatitis, and primary biliary cirrhosis. PAS III includes autoimmune thyroid disease plus another autoimmune disorder in the absence of Addison disease. If the other autoimmune disorder is insulin-dependent diabetes mellitus, it is designated as type IIIa. Type IIIb involves pernicious anemia, whereas type IIIc includes vitiligo, alopecia, and/or other organ-specific autoimmune disease. Our patient had Hashimoto thyroiditis, alopecia, adult-onset Still disease, vasculitis, ANCA-mediated crescentic glomerulonephritis, and hyperparathyroidism. Accordingly, she was classified as type IIIc. By reviewing the literature (Table 3), we confirm that this is a rare combination that has never been reported. Moss et al[6] described a patient with type IIIc PAS who presented with antibasement membrane antibody disease. They incorporated the antibasement membrane antibody disease into the spectrum of PAS. Shimomura et al[10] reported a case with PAS III associated with Sjögren syndrome and autoimmune neutropenia. They considered autoimmune disorders as the cause of this condition. In our case, multiple autoimmune disorders including autoimmune thyroiditis, adult-onset Still disease, and positive autoantibodies might be associated with the onset of vasculitis and ANCA-mediated crescentic glomerulonephritis. At present, the mechanism of PAS is unclear, but its occurrence is associated with the genetic susceptibility associated with the human leukocyte antigen.[63] Tadmor et al[64] have hypothesized that organs derived from the same embryonal germ layer share

Table 3

Summary of reported cases with autoimmune polyglandular syndrome type III.

Year	Authors	Sex/age	Clinical manifestation	Type
1989	Takamatsu et al[3]	F/40	Type 1 diabetes mellitus Hashimoto thyroiditis Relapsing polychondritis	PAS IIIa
1993	Papadopoulos and Hallengren[4]	F/52	Type 1 diabetes mellitus Hashimoto thyroiditis Graves disease Vitiligo, celiac disease Sarcoidosis	PAS IIIa
1994	Kam et al[5]	F/24	Hypothyroidism Pernicious anemia Vitiligo	PAS IIIb
1994	Moss et al[6]	N/A	Antibasement membrane antibody disease	PAS IIIc
1995	Rodríguez Quiroz et al[7]	F/16	Type 1 diabetes mellitus Chronic atrophic gastritis Hypothyroidism Rheumatoid arthritis	PAS IIIa
2000	Berberoğlu et al[8]	F/14	Thyrotoxicosis Hashimoto thyroiditis Autoimmune hemolytic anemia Focal segmental glomerulonephritis Hypoparathyroidism Munchausen syndrome	PAS IIIc
2003	Papi et al[9]	F/41	Thyroid hemiagenesis Hashimoto thyroiditis Alopecia areata Premature ovarian failure	PAS IIIc
2003	Shimomura et al[10]	F/57	Type 1 diabetes mellitus Sjögren syndrome Graves disease Autoimmune neutropenia Cutaneous lupus erythematosus	PAS IIIa
2004	Bahceci et al[11]	F/24	Common variable immunodeficiency Membranoproliferative glomerulonephritis Hypergonadotropic hypogonadism Insufficient growth hormone response Thyroid autoimmunity	PAS IIIc
2004	Ugur-Altun et al[12]	N/A	Thyroid autoimmunity Autoimmune leukopenia	PAS IIIc
2006	Mikitiuk and Voropaï[13]	N/A	Thyroiditis	None
2006	Oki et al[14]	F/58	Graves disease Type 1 diabetes mellitus Autoimmune hepatitis	PAS IIIa
2006	Funauchi et al[15]	F/51	Type 1 diabetes mellitus Sjögren syndrome Autoimmune exocrinopathy Systemic lupus erythematosus	PAS IIIa
2007	Molina-Garrido et al[16]	M/54	Hyperaldosteronism Vitiligo Autoimmune thyroid disease	PAS IIIc
2007	Rodríguez-Martín et al[17]	F/28	Vitiligo Autoimmune hypothyroidism Pernicious anaemia	PAS IIIb
2008	Elefsiniotis et al[18]	N/A	Insulin-dependent diabetes mellitus Autoimmune thyroiditis Atrophic gastritis Pernicious anemia Immunologic thrombocytopenic purpura	PAS III (A + B)
2008	Lubińska et al[19]	F/20	Hashimoto thyroiditis	PAS IIIc

(*continued*)

Table 3
(continued).

Year	Authors	Sex/ age	Clinical manifestation	Type
			Myasthenia gravis	
			Vascular hemophilia	
2009	Briscoe and Mezei[20]	M/37	Type 1 diabetes mellitus	None
			Pernicious anaemia	
			Ocular myasthenia gravis	
2009	Futagami et al[21]	F/15	Vogt-Koyanagi-Harada disease	PAS IIIa
			Insulin-dependent diabetes mellitus	
			Nephrotic syndrome	
			Vitiligo	
2009	Sheehan and Islam[22]	M/43	Spontaneous return to euthyroidism	None
			Ulcerative colitis	
			Alopecia areata	
2010	Fujioka et al[23]	F/55	Type 1 diabetes mellitus	PAS IIIa
			Graves disease	
2010	Mazokopakis et al[24]	F/38	Type 1 diabetes mellitus	PAS IIIa
			Hashimoto thyroiditis	
			Autoimmune gastritis	
2010	Turkoglu et al[25]	M/12	Hashimoto thyroiditis	PAS IIIc
			Vitiligo	
			Alopecia universalis	
2010	Quintyne et al[26]	M/33	Autoimmune hypothyroidism	PAS IIIc
			Alopecia universalis	
			Pituitary hyperplasia	
2010	Quintos et al[27]	M/3	Type 1 diabetes mellitus	PAS IIIa
			Graves disease	
			Growth hormone deficiency	
2010	Farkas et al[28]	M/37	Insulin-dependent diabetes mellitus	PAS IIIc
			Ulcerative colitis	
			Hashimoto thyroiditis	
			Vitiligo	
			Rheumatoid arthritis	
2011	Krysiak et al[29]	N/A	Cushing syndrome	None
			Autoimmune endocrine disorders	
2011	Kleinschmidt et al[30]	N/A	Insulin-dependent diabetes mellitus	PAS IIIa
			Graves disease	
2011	Kamitani et al[31]	N/A	Thyrotoxic crisis	None
			Diabetic coma	
2011	Trivedi et al[32]	F/17	Insulin-dependent diabetes mellitus	PAS IIIa
			Hypothyroidism	
		M/19	Insulin-dependent diabetes mellitus	PAS IIIa
			Hypothyroidism	
2011	Choudhury et al[33]	F/35	Hypothyroidism	PAS IIIc
			Hypoparathyroidism	
			Intestinal lymphangiectasia	
2012	Yokote et al[34]	F/73	Type 1 diabetes mellitus	PAS IIIa
			Chronic thyroiditis	
			Late-onset multiple sclerosis	
2013	Mizokami et al[35]	F/41	Type 1 diabetes mellitus	PAS IIIa
			Graves disease	
		F/27	Type 1 diabetes mellitus	PAS IIIa
			Graves disease	
2013	Iwahashi et al[36]	F/42	Type 1 diabetes mellitus	PAS IIIa
			Chronic thyroiditis	
			Idiopathic portal hypertension	
2013	Kanazawa et al[37]	M/40	Hyperthyroidism	PAS IIIa
			Insulin-dependent diabetes mellitus	
			Antiphospholipid antibody syndrome	
2013	Wei et al[38]	F/62	Pernicious anemia	PAS IIIb
			Autoimmune thyroiditis	
2013	Melcescu et al[39]	F/34	Graves disease	PAS IIIc
			Hypoparathyroidism	
			Alopecia	
			Systemic lupus erythematosus	
2014	Kasznicki and Drzewoski[40]	F/37	Hashimoto thyroiditis	PAS IIIa
			Type 1 diabetes mellitus	
			Vitiligo	
			Autoimmune urticaria	
2014	Ocampo Chaparro et al[41]	M/92	Insulin-dependent diabetes mellitus	PAS IIIa
			Hypothyroidism	
2014	Innico et al[42]	F/51	Autoimmune hypothyroidism	PAS IIIc
			Celiac disease	
			Sicca syndrome	
2014	Hadwen et al[43]	F/30	Insulin-dependent diabetes mellitus	PAS IIIa
			Graves disease	
			Vitiligo	
			Autoimmune cardiomyopathy	
2014	Batra et al[44]	F/6	Type 1 diabetes mellitus	PAS IIIa
			Anti-TPO-positive hypothyroidism	
2014	Duman et al[45]	M/1	Hashimoto thyroiditis	PAS IIIc
			Alopecia	
			Chronic urticaria	
			Myasthenia gravis	
2014	Büyükçelik et al[46]	F/10	Autoimmune thyroiditis	PAS IIIc
			Ectodermal dysplasia	
			Immune deficiency	
			Hemolytic-uremic syndrome	
2014	Norasyikin et al[47]	F/62	Autoimmune thyroiditis	PAS IIIb
			Pernicious anemia	
2014	Kim et al[48]	F/32	Type 1 diabetes mellitus	PAS IIIa
			Autoimmune thyroiditis	
			Primary hypoparathyroidism	
2015	Krysiak and Okopień[49]	F	Insulin-dependent diabetes mellitus	PAS IIIa
			Autoimmune thyroiditis	
2015	De Marchi et al[50]	F/51	Hashimoto thyroiditis	APS III
			Pernicious anemia	(A + B)
			Autoimmune chronic urticaria	
			Myasthenia gravis	
			Type 1 diabetes mellitus	
2015	de Sousa et al[51]	F/34	Autoimmune thyroiditis	PAS IIIb
			Pernicious anemia	
2015	Kurozumi et al[52]	M/40	Type 1 diabetes mellitus	PAS IIIa
			Graves disease	
2015	Colucci et al[53]	N/A	Vogt-Koyanagi-Harada syndrome	PAS IIIc
			Common variable immunodeficiency	
2016	Pecorino et al[54]	F/34	Type 1 diabetes mellitus	PAS IIIa
			Autoimmune Hashimoto thyroiditis	
			Celiac disease	
2016	Capo and Amerio[55]	F/52	Autoimmune thyroiditis	PAS IIIc
			Vitiligo	
			Alopecia areata	
2016	Horsey et al[56]	F/71	Autoimmune thyroid disease	PAS IIIb
			Pernicious anemia	
			Deep vein thrombosis	
2016	Takahashi et al[57]	F/66	Graves disease	PAS IIIb
			Pernicious anemia	
2017	Kolkhir et al[58]	F/54	Autoimmune thyroiditis	PAS IIIc
		F/34	Vitiligo	
		F/49	Chronic spontaneous urticaria	
		F/61		
		F/67		
		M/55		
2018	Allam and Elzawawy[59]	F/22	Hashimoto thyroiditis	PAS III
			Autoimmune gastritis	(B + C)
			Autoimmune hepatitis	
			Vitiligo	
		M/28	Type 1 diabetes mellitus	PAS IIIa
			Graves disease	
2018	Morita et al[60]	M/6	Hashimoto thyroiditis	PAS III
			Type 1 diabetes mellitus	(A + C)
			Alopecia	
			Vitiligo	
2018	Iijima et al[61]	F/65	Type 1 diabetes mellitus	PAS IIIa
			Hashimoto thyroiditis	
			Pulmonary arterial hypertension	
2018	Jamiołkowska and Bossowski[62]	F/15	Autoimmune thyroiditis	PAS IIIc
			Graves disease	
			Myasthenia gravis	
2019	Our case	F/51	Hashimoto thyroiditis	PAS IIIc
			Alopecia	
			Hyperparathyreosis	
			Adult Still disease	
			Vasculitis	
			ANCA-mediated crescentic Glomerulonephritis	

F = female, M = male, NA = not available.

common specific antigens. Recent studies have shown that polymorphisms of the T-cell regulatory gene (cytotoxic T-lymphocyte-associated antigen 4) are associated with PAS.[65] Evidently, the immunological mechanisms are crucial in the development of the autoimmune disease, and the intervention of activated self-reacting T cell is considered to be necessary in the majority of the cases to achieve complete destruction of the target organ.[66]

Therapies regarding the different components of PAS III are similar whether they occur as single or in multiple associations with other autoimmune diseases. However, it is worth noting that Hashimoto disease can present as transient thyrotoxicosis; hence, antithyroid drugs and radiotherapy with iodine-131 must be carefully considered when treating Hashimoto disease. Additionally, the thyroid hormone replacement therapy in patients with autoimmune hypothyroidism may result in adrenal failure because thyroxine may enhance hepatic corticosteroid metabolism. Thus, before initiating the therapy with thyroxine, it is crucial to investigate the possible coexistence of an underlying adrenal insufficiency.[67]

4. Conclusions

We report a patient with Hashimoto thyroiditis, adult-onset Still disease, alopecia, vasculitis, ANCA-mediated crescentic glomerulonephritis, and hyperparathyroidism, which is a very rare combination. We present this case as evidence for the coexistence of several different immune-mediated diseases in the clinical context of a PAS IIIc.

Author contributions

Data curation: Shiyuan Tian.
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Writing – original draft: Shiyuan Tian.
Writing – review & editing: Rui Liu.

References

[1] Neufeld M, Blizzard RM. Pinchera A, Doniach D, Fenzi GF, Baschieri L. Polyglandular autoimmune diseases. Symposium on Autoimmune Aspects of Endocrine Disorders New York: Academic Press; 1980;357–65.
[2] Eisenbarth GS, Gottlieb PA. Autoimmune polyendocrine syndromes. N Engl J Med 2004;350:2068–79.
[3] Takamatsu K, Nishiyama T, Nakauchi Y, et al. A case of insulin dependent diabetes mellitus associated with relapsing polychondritis, Hashimoto's thyroiditis and pituitary adrenocortical insufficiency in succession. Jpn J Med 1989;28:232–6.
[4] Papadopoulos KI, Hallengren B. Polyglandular autoimmune syndrome type III associated with coeliac disease and sarcoidosis. Postgrad Med J 1993;69:72–5.
[5] Kam T, Birmingham CL, Goldner EM. Polyglandular autoimmune syndrome and anorexia nervosa. Int J Eat Disord 1994;16:101–3.
[6] Moss M, Neff TA, Colby TV, et al. Diffuse alveolar hemorrhage due to antibasement membrane antibody disease appearing with a polyglandular autoimmune syndrome. Chest 1994;105:296–8.
[7] Rodríguez Quiroz F, Berrón Pérez R, Ortega Martell JA, et al. Type III polyglandular autoimmune syndrome. Report of a case. Allergol Immunopathol (Madr) 1995;23:251–3.
[8] Berberoğlu M, Ocal G, Cetinkaya E, et al. Polyglandular autoimmune syndrome accompanied by Munchausen syndrome. Pediatr Int 2000;42:386–8.
[9] Papi G, Salvatori R, Ferretti G, et al. Thyroid hemiagenesis and autoimmune polyglandular syndrome type III. J Endocrinol Invest 2003;26:1160–1.
[10] Shimomura H, Nakase Y, Furuta H, et al. A rare case of autoimmune polyglandular syndrome type 3. Diabetes Res Clin Pract 2003;61:103–8.
[11] Bahceci M1, Tuzcu A, Pasa S, et al. Polyglandular autoimmune syndrome type III accompanied by common variable immunodeficiency. Gynecol Endocrinol 2004;19:47–50.
[12] Ugur-Altun B, Arikan E, Guldiken S, et al. Autoimmune polyglandular syndrome type III in monozygotic twins: a case report. Acta Clin Belg 2004;59:225–8.
[13] Mikitiuk MR, Voropaĭ TI. The case of autoimmune polyglandular syndrome of type III. Lik Sprava 2006;5:67–8.
[14] Oki K, Yamane K, Koide J, et al. A case of polyglandular autoimmune syndrome type III complicated with autoimmune hepatitis. Endocr J 2006;53:705–9.
[15] Funauchi M, Tamaki C, Yamagata T, et al. A case of autoimmune polyglandular syndrome type III with a slowly progressive form of type-1 diabetes mellitus that manifested in the course of autoimmune diseases. Scand J Rheumatol 2006;35:81–2.
[16] Molina-Garrido MJ, Enríquez R, Mora-Rufete A, et al. Primary hyperaldosteronism associated with vitiligo vulgaris and autoimmune hypothyroidism. Am J Med Sci 2007;333:178–80.
[17] Rodríguez-Martín M, Sáez-Rodríguez M, Carnerero-Rodríguez A, et al. Coincidental presentation of vitiligo and psoriasis in a patient with polyglandular autoimmune syndrome. Clin Exp Dermatol 2007;32:453.
[18] Elefsiniotis IS, Papatsimpas G, Liatsos GD, et al. Atypical autoimmune polyglandular syndrome type 3 overlapped by chronic HCV infection resulting in carcinogenesis and fatal infection. South Med J 2008;10:756–8.
[19] Lubińska M, Swiatkowska-Stodulska R, Kazimierska E, et al. Acquired von Willebrand's disease in the course of severe primary hypothyroidism in a patient with autoimmune polyglandular syndrome type 3. Endokrynol Pol 2008;59:34–7.
[20] Briscoe NK, Mezei MM. Polyglandular autoimmune syndrome type 3 in a patient with ocular myasthenia gravis. Muscle Nerve 2009;40:1064–5.
[21] Futagami Y, Sugita S, Fujimaki T, et al. Bilateral anterior granulomatous keratouveitis with sunset glow fundus in a patient with autoimmune polyglandular syndrome. Ocul Immunol Inflamm 2009;17:88–90.
[22] Sheehan MT, Islam R. Silent thyroiditis, isolated corticotropin deficiency, and alopecia universalis in a patient with ulcerative colitis and elevated levels of plasma factor VIII: an unusual case of autoimmune polyglandular syndrome type 3. Endocr Pract 2009;15:138–42.
[23] Fujioka T, Honda M, Yoshizaki T, et al. A case of type 1 diabetes onset and recurrence of Graves' disease during pegylated interferon-(plus ribavirin treatment for chronic hepatitis C. Intern Med 2010;49:1987–90.
[24] Mazokopakis EE, Karefilakis CM, Batistakis AG, et al. High serum levels of calcitonin are not pathognomonic of medullary thyroid carcinoma and may indicate polyglandular autoimmune syndrome III. Hell J Nucl Med 2010;13:67–8.
[25] Turkoglu Z, Kavala M, Kolcak O, et al. Autoimmune polyglandular syndrome-3C in a child. Dermatol Online J 2010;16:8.
[26] Quintyne KI, Barratt N, O'Donoghue L, et al. Alopecia universalis, hypothyroidism and pituitary hyperplasia: polyglandular autoimmune syndrome III in a patient in remission from treated Hodgkin lymphoma. BMJ Case Rep 2010;2010.
[27] Quintos JB, Grover M, Boney CM, et al. Autoimmune polyglandular syndrome type 3 and growth hormone deficiency. Pediatr Diabetes 2010;11:438–42.
[28] Farkas K, Nagy F, Kovács L, et al. Ulcerative colitis and primary sclerosing cholangitis as part of autoimmune polyglandular syndrome type III. Inflamm Bowel Dis 2010;16:10–1.
[29] Krysiak R, Szkróbka W, Okopień B. Autoimmune polyendocrine syndrome type 3 in a patient after surgical treatment of Cushing syndrome. Wiad Lek 2011;64:193–7.
[30] Kleinschmidt K, Martoni A, Masetti R, et al. Autoimmune polyglandular syndrome type III after haploidentical hematopoietic stem cell transplantation in a child with acute myeloid leukemia. Pediatr Blood Cancer 2012;59:341.
[31] Kamitani Y, Harada Y, Uchikura T, et al. Case report; autoimmune polyendocrine syndrome type3 with thyrotoxic crisis and diabetic coma. Nihon Naika Gakkai Zasshi 2011;100:1051–3.
[32] Trivedi HL, Thakkar UG, Vanikar AV, et al. Treatment of polyglandular autoimmune syndrome type 3 using co-transplantation of insulin-secreting mesenchymal stem cells and haematopoietic stem cells. BMJ Case Rep 2011;2011.
[33] Choudhury BK, Saiki UK, Sarm D, et al. Intestinal lymphangiectasia in a patient with autoimmune polyglandular syndrome type III. J Assoc Physicians India 2011;59:729–31.

[34] 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.
[35] Mizokami T, Yamauchi A, Sato Y, et al. Simultaneous occurrence of type 1 diabetes mellitus and Graves' disease: a report of two cases and a review of the literature. Intern Med 2013;52:2537–43.
[36] Iwahashi A, Nakatani Y, Hirobata T, et al. Autoimmune polyglandular syndrome III in a patient with idiopathic portal hypertension. Intern Med 2013;52:1375–8.
[37] Kanazawa Y, Matsuo R, Fukushima Y, et al. Progression of right internal carotid artery stenosis in ischemic stroke patient with autoimmune polyglandular syndrome: a case report. Rinsho Shinkeigaku 2013;53:531–5.
[38] Wei R, Chang A, Rockoff A. Polyglandular autoimmune syndrome disguised as mental illness. BMJ Case Rep 2013;2013.
[39] Melcescu E, Kemp EH, Majithia V, et al. Graves' disease, hypoparathyroidism, systemic lupus erythematosus, alopecia, and angioedema: autoimmune polyglandular syndrome variant or coincidence? Int J Immunopathol Pharmacol 2013;26:217–22.
[40] 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.
[41] Ocampo Chaparro JM, Reyes Ortiz CA, Ramírez M, et al. Type III polyglandular autoimmune syndrome: a case report. Rev Esp Geriatr Gerontol 2014;49:244–5.
[42] Innico G, Frassetti N, Coppola B, et al. Autoimmune polyglandular syndrome in a woman of 51 years. Eur Rev Med Pharmacol Sci 2014;18:1717–9.
[43] Hadwen TI, Foster K, Buchanan J, et al. A case of nonischemic cardiomyopathy associated with autoimmune polyglandular syndrome type III. Endocr Pract 2014;20:183–6.
[44] Batra P, Singhal R, Shah D. Diabetic lipemia presenting as eruptive xanthomas in a child with autoimmune polyglandular syndrome type IIIa. J Pediatr Endocrinol Metab 2014;27:569–71.
[45] Duman O, Koken R, Baran RT, et al. Infantile anti-MuSK positive myasthenia gravis in a patient with autoimmune polyendocrinopathy type 3. Eur J Paediatr Neurol 2014;18:526–8.
[46] Büyükçelik M, Keskin M, Keskin Ö, et al. Autoimmune polyglandular syndrome type 3c with ectodermal dysplasia, immune deficiency and hemolytic-uremic syndrome. J Clin Res Pediatr Endocrinol 2014;6:47–50.
[47] Norasyikin AW, Rozita M, Mohd Johan MJ, et al. Autoimmune polyglandular syndrome presenting with jaundice and thrombocytopenia. Med Princ Pract 2014;23:387–9.
[48] Kim SJ, Kim SY, Kim HB, et al. Polyglandular autoimmune syndrome type III with primary hypoparathyroidism. Endocrinol Metab (Seoul) 2013;28:236–40.
[49] Krysiak R, Okopień B. Coexistence of autoimmune polyglandular syndrome type 3 with diabetes insipidus. Wiad Lek 2015;68:204–7.
[50] 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;52:440–4.
[51] de Sousa AWP, da Silva VM, Fernandes PA. Polyglandular syndrome type III and severe peripheral neuropathy: an unusual association. GE Port J Gastroenterol 2015;22:15–8.
[52] Kurozumi A, Okada Y, Arao T, et al. Induction of thyroid remission using rituximab in a patient with type 3 autoimmune polyglandular syndrome including Graves' disease and type 1 diabetes mellitus: a case report. Endocr J 2015;62:69–75.
[53] Colucci R, Galeone M, Conti R, et al. Autoimmune polyglandular type IIIc syndrome associated with Vogt-Koyanagi-Harada syndrome and common variable immunodeficiency. G Ital Dermatol Venereol 2015;150:633–5.
[54] Pecorino B, Teodoro MC, Scollo P. Polyglandular autoimmune syndrome in pregnancy: case report. Ital J Gynaecol Obstet 2016;28:35–40.
[55] Capo A, Amerio P. Polyglandular autoimmune syndrome type III with a prevalence of cutaneous features. Clin Exp Dermatol 2017;42:61–3.
[56] Horsey M, Hogan P, Oliver T. Deep vein thrombosis, an unreported first manifestation of polyglandular autoimmune syndrome type III. Endocrinol Diabetes Metab Case Rep 2016;2016.
[57] Takahashi T, Hara K, Takayoshi T, et al. Case Report; Gastric mucosa in patients with autoimmune thyroiditis. (Discussion about a case of autoimmune polyendocrine syndrome 3B). Nihon Naika Gakkai Zasshi 2016;105:81–5.
[58] Kolkhir P, Pogorelov D, Kochergin N. Chronic spontaneous urticaria associated with vitiligo and thyroiditis (autoimmune polyglandular syndrome IIIC): case series. Int J Dermatol 2017;56:e89–90.
[59] Allam MM, Elzawawy HTH. Induction of remission in autoimmune polyglandular syndrome type three (APS III): an old drug with new perspectives. Clin Case Rep 2018;6:2178–84.
[60] Morita C, Yanase T, Shiohara T, et al. Aggressive treatment in paediatric or young patients with drug-induced hypersensitivity syndrome (DiHS)/drug reaction with eosinophilia and systemic symptoms (DRESS) is associated with future development of type III polyglandular autoimmune syndrome. BMJ Case Rep 2018;2018:
[61] Iijima T, Niitani T, Tanaka S, et al. Concurrent variant type 3 autoimmune polyglandular syndrome and pulmonary arterial hypertension in a Japanese woman. Endocr J 2018;65:493–8.
[62] Jamiołkowska M, Bossowski A. 15-Year old girl with APS type IIIc, 12 months post-thymectomy remission of myasthenia. Pediatr Endocrinol Diabetes Metab 2017;23:49–55.
[63] Flesch BK, Matheis N, Alt T, et al. HLA class II haplotypes differentiate between the adult autoimmune polyglandular syndrome types II and III. J Clin Endocrinol Metab 2014;99:177–82.
[64] Tadmor B, Putterman C, Naparstek Y. Embryonal germ-layer antigens: target for autoimmunity. Lancet 1992;339:975–8.
[65] Ueda H, Howson JM, Espositol L, et al. Association of the T-cell regulatory gene CTLA4 with susceptibility to autoimmune disease. Nature 2003;423:506–11.
[66] Roep BO. Autoreactive T cells in endocrine/organ-specific autoimmunity: why has progress been so slow? Springer Semin Immunopathol 2002;24:261–71.
[67] Schatz DA, Winter WE. Autoimmune polyglandular syndrome II. Clinical syndrome and treatment. Endocrinol Metab Clin N Am 2002;31:339–52.