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AUTOIMMUNE POLYGLANDULAR SYNDROME TYPE 3B: A KEY TO DIAGNOSING AUTOIMMUNE GASTRITIS AND ASYMPTOMATIC PRIMARY BILIARY CHOLANGITIS

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ABSTRACT

Background: Autoimmune polyglandular syndrome type 3 (APS-3) encompasses autoimmune thyroid disease and other autoimmune disorders. APS-3 is further categorized into four subtypes, with APS-3B involving gastrointestinal autoimmune diseases. In this case, we diagnosed autoimmune gastritis, a condition challenging to identify based on endoscopic findings alone, and asymptomatic primary biliary cholangitis (PBC) through the recognition of APS-3B.

Case report: An 84-year-old female patient presented with forgetfulness and a history of Hashimoto's disease. Although endoscopy revealed pan-atrophic gastritis, autoimmune gastritis was suspected rather than *Helicobacter pylori* infection due to consideration of the APS-3 framework. Specific observations, including adherent mucus and remnants of oxyntic mucosa, guided tests for anti-endogenous antibodies, confirming autoimmune gastritis. Recognizing APS-3B prompted further evaluation for PBC, including measurement of anti-mitochondrial M2 antibody, which led to the diagnosis of asymptomatic PBC.

Conclusion: Recognition of APS-3 offers a valuable framework for the differential diagnosis of autoimmune diseases.

KEYWORDS

Autoimmune polyglandular syndrome type 3, diagnosis, autoimmune gastritis, primary biliary cholangitis

LEARNING POINTS

- Autoimmune thyroid disease in a patient should raise suspicion for autoimmune polyglandular syndrome type 3 (APS-3) and other potential autoimmune conditions.
- If APS-3 is diagnosed, further classification is recommended, along with a thorough search for additional autoimmune diseases.
- APS-3 serves as a framework for the differential diagnosis of autoimmune diseases.

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BACKGROUND

Autoimmune polyglandular syndrome (APS) was first classified by Neufeld and Blizzard in 1980[1]. This syndrome involves the disruption of at least two endocrine glands due to an autoimmune mechanism and is categorized into four main types: APS type 1 (APS-1) is characterized by chronic candidiasis, chronic hypoparathyroidism, and Addison's disease; APS-2 includes Addison's disease along with autoimmune thyroid disease and/or type 1 diabetes mellitus; APS-3 is defined by the coexistence of autoimmune thyroid diseases with other autoimmune conditions, excluding Addison's disease; APS-4 encompasses two or more autoimmune diseases that do not fit the criteria for APS-1, APS-2, or APS-3 *(Table 1)*[1]. APS-3 is further divided into four subtypes *(Table 1)*[2,3]. For instance, a patient with autoimmune thyroid disease who also has autoimmune gastritis and primary biliary cholangitis (PBC) would be classified as APS-3B.

The diagnosis of autoimmune gastritis poses challenges for general physicians for two main reasons. First, the endoscopic findings associated with autoimmune gastritis - such as pan-atrophy (90.1%), hyperplastic polyps (21.1%), and sticky, adherent, dense mucus (32.4%)[4] - are often similar to those seen in common *Helicobacter pylori* (HP) infections. Second, the urea breath test (UBT), a widely recommended, non-invasive diagnostic tool with high sensitivity (97.7–100%) and specificity (97.9–100%)[5], can yield false-positive results in cases of autoimmune gastritis. This occurs because urease-producing commensal bacteria can mimic HP infection in the absence of HP itself[6]. Consequently, autoimmune gastritis is sometimes misdiagnosed as HP infection, leading to repeated eradication therapy. Notably, the likelihood of autoimmune gastritis increases with repeated failures of HP eradication therapy: 2.1% of patients who failed eradication therapy once and 18.2% of those who failed it twice were eventually diagnosed with autoimmune gastritis[7].

The diagnosis of PBC is also challenging, as it is often asymptomatic in its early stages. Moreover, approximately 10% of PBC cases lack anti-mitochondrial antibodies, which are a key diagnostic criterion[8].

Recognizing APS-3 can facilitate the consideration of an association between autoimmune thyroid disease and other autoimmune disorders. Additionally, understanding the subclasses of APS-3 can help narrow the differential diagnosis of autoimmune diseases.

Here, we report a patient with Hashimoto's disease in whom APS-3B was suspected, leading to the diagnosis of autoimmune gastritis and asymptomatic PBC. This case highlights the utility of APS-3 as a framework for the differential diagnosis of autoimmune diseases.

CASE DESCRIPTION

An 84-year-old female patient with mild forgetfulness sought a cognitive function evaluation as part of the application for long-term care insurance. The patient reported a limited history of regular visits to an internal medicine clinic or undergoing physical examinations.

The patient was evaluated for treatable causes of mild forgetfulness, including potentially reversible dementias, intracranial diseases, and autoimmune conditions such as Hashimoto's disease and systemic lupus erythematosus (SLE).

Physical examination revealed a mildly enlarged but non-tender thyroid gland, with no bradycardia or leg oedema. Blood tests showed macrocytic anaemia with haemoglobin (Hb) at 11.0 g/dl, mean corpuscular volume (MCV) at 125 fl and low vitamin B12 levels (139 pg/ml). Thyroid function tests were within the reference range for thyroid-stimulating hormone (TSH) and free thyroxine (FT4) however, anti-thyroid peroxidase (TPO) antibody was markedly elevated (>2000 IU/ml).

Thyroid ultrasonography demonstrated diffuse thyroid

APS	Disease	Specific regions
APS-1	Chronic candidiasis, chronic hypoparathyroidism, and Addison's disease (two or three conditions present)	-
APS-2	Addison's disease with autoimmune thyroid diseases and/or type 1 diabetes mellitus	-
APS-3A	Autoimmune thyroid diseases with type 1 diabetes mellitus (excluding Addison's disease)	Endocrine diseases
APS-3B	Autoimmune thyroid diseases with autoimmune gastritis and/or celiac disease and/or inflammatory bowel disease and/or autoimmune hepatitis and/or primary biliary cholangitis	Gastrointestinal diseases
APS-3C	Autoimmune thyroid diseases with vitiligo and/or alopecia and/or myasthenia gravis and/or immune thrombocytopenic purpura and/or autoimmune haemolytic anaemia and/or antiphospholipid antibody syndrome and/or stiff-person syndrome and/or multiple sclerosis	Cutaneous/ hematopoietic/ neurogenic diseases
APS-3D	Autoimmune thyroid diseases with autoimmune gastritis and/or systemic lupus erythematosus and/or mixed connective tissue disease and/or rheumatoid arthritis and/or systemic sclerosis and/or Sjögren's syndrome and/or vasculitis	Collagen diseases
APS-4	Two or more autoimmune diseases that do not fit APS-1, APS-2, or APS-3	-

Table 1. Classification of autoimmune polyglandular syndrome (APS).

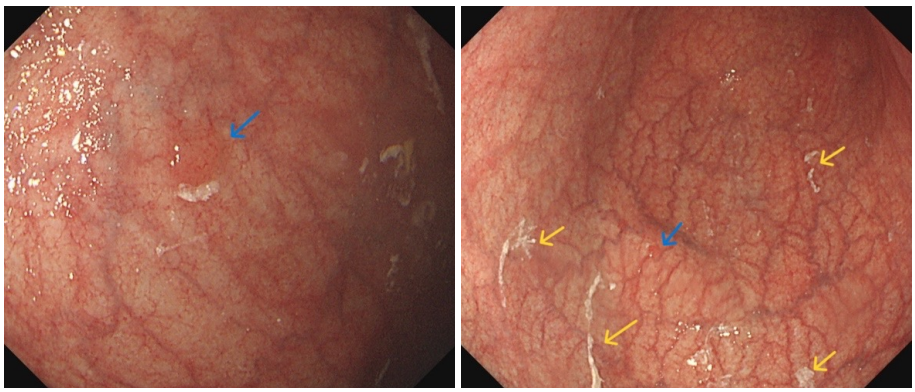


Figure 1. Endoscopy shows pan-atrophy, remnants of oxyntic mucosa (blue arrow), and sticky, adherent, dense mucous (yellow arrows).

enlargement without evidence of mass formation or increased blood flow. Endoscopic evaluation for anaemia revealed pan-atrophy, adherent mucus, and residual fundic mucosa *(Fig. 1)* but no masses or bleeding lesions suggestive of malignancy.

Additional blood tests showed a gastrin level of 481 pmol/l; antinuclear antibodies at a titre of 1:1280 (centromere pattern 1:1280, speckled pattern 1:80); negative results for anti-RNA polymerase III antibody, anti-Scl-70 antibody, anti-SS-A antibody, anti-SS-B antibody, and anti-smooth muscle antibody; anti-centromere antibody at 383 IU/ml; anti-intrinsic factor antibody positive; and HP IgG at 3 U/ml *(Table 2)*. Additional testing revealed an anti-mitochondrial M2 antibody level of 415 *(Table 2)*.

No treatable disease was identified as the cause of forgetfulness, which was attributed to aging. Based on diffuse thyroid gland enlargement and a positive anti-TPO antibody test, a diagnosis of Hashimoto's thyroiditis was made. Endoscopy revealed atrophic gastritis, sticky, adherent mucous, remnants of oxyntic mucosa, and a positive anti-intrinsic factor antibody test, leading to the diagnosis of autoimmune gastritis. Vitamin B12 deficiency anaemia was deemed secondary to autoimmune gastritis. The diagnosis of PBC was confirmed based on transient elevation of alkaline phosphatase (ALP) and a positive anti-mitochondrial M2 antibody test.

For vitamin B12 deficiency anaemia, the patient was started on 1 mg of oral vitamin B12. Hashimoto's thyroiditis was monitored, as thyroid function remained normal. Ursodeoxycholic acid will be administered if hepatobiliary enzymes rise in the future, to manage the progression of cirrhosis.

One month after initiating oral vitamin B12 treatment, anaemia improved, with Hb 12.9 g/dl and MCV 109.4 fl. The patient will continue to undergo regular upper gastrointestinal endoscopic examinations to monitor liver and thyroid function and detect complications of PBC, such as varices, at an early stage.

DISCUSSION

This case indicates that when a patient has autoimmune thyroid disease, APS-3 should be considered, and the presence of other autoimmune diseases should be suspected. Additionally, once the subtype of APS-3 is

Laboratory investigations	Result
Haemoglobin (g/dl)	11.0
Red blood cells (cells/µl)	2,460,000
Mean corpuscular volume (fl)	125.2
White blood cells (cells/µl)	4,670
Platelets (cells/µl)	114,000
Total protein (g/dl)	6.8
Albumin (g/dl)	3.9
Aspartate aminotransferase (U/l)	24
Alanine aminotransferase (U/l)	6
Lactate dehydrogenase (U/l)	234
Alkaline phosphatase (U/l)	80
Blood urea nitrogen (mg/dl)	17.4
Creatinine (U/l)	0.55
Sodium, Na (mEq/l)	140
Potassium, K (mEq/l)	4.2
Chloride, Cl (mEq/l)	105
Thyroid-stimulating hormone (µU/ml)	1.74
Free thyroxine (ng/dl)	0.83
Vitamin B12 (pg/ml)	139
Gastrin (pmol/l)	481
Anti-TPO antibody (U/ml)	>2,000
Anti-thyroglobulin antibody (U/ml)	12.8
Antinuclear antibodies	1280
Anti U1-RNP antibody	-
Anti-RNA polymerase 3 antibody	-
Anti-Smith antibody	-
Anti-Scl-70 antibody	-
Anti-centromere antibody (U/ml)	383
Anti-ARS antibody	-
Anti-SS-A antibody	-
Anti-SS-B antibody	-
Anti-smooth muscle antibody	-
Anti-mitochondrial antibody	20
Anti-mitochondrial M2 antibody	415
Anti-intrinsic antibody	+
Helicobacter pylori IgG (U/ml)	3

Abbreviations: TPO, thyroid peroxidase; RNP, ribonucleoprotein; RNA, ribonucleic acid; Scl, scleroderma; ARS, aminoacyl tRNA synthetase.

Table 2. Results of the investigations.

determined, it may help physician focus on specific regions of autoimmune disease and inform the differential diagnosis. This is important as the rates of other autoimmune diseases in autoimmune thyroid diseases were found to be 9.67% in Graves' disease and 14.3% in Hashimoto's disease[9]. It has also been reported that one-third of patients with autoimmune thyroid diseases have autoimmune gastritis[10]. In the present case, the patient had Hashimoto's disease, and upon diagnosing atrophic gastritis, we suspected autoimmune gastritis rather than HP infection. Moreover, since the classification of APS-3 subtypes is based on disease group, it can help narrow down the differential diagnosis within specific groups of autoimmune diseases. APS-3A is characterized by autoimmune thyroid diseases and type 1 diabetes mellitus, both endocrine diseases. APS-3B includes autoimmune thyroid diseases and autoimmune gastritis, celiac disease, inflammatory bowel disease, autoimmune hepatitis, or primary biliary cholangitis, all gastrointestinal diseases. APS-3C encompasses autoimmune thyroid diseases and vitiligo, alopecia, myasthenia gravis, idiopathic thrombocytopenic purpura, autoimmune haemolytic anaemia, antiphospholipid antibody syndrome, stiff-person syndrome, and multiple sclerosis, which are cutaneous, hematopoietic, or neurogenic diseases. APS-3D includes autoimmune thyroid diseases and autoimmune gastritis, SLE, mixed connective tissue disease, rheumatoid arthritis, systemic sclerosis, Sjögren's syndrome, or vasculitis, all of which are collagen diseases *(Table 1)*. Although the immunological similarities and differences between the subtypes remain unclear[3], it has been reported that HLA-DR3 is a susceptibility gene for APS-3A[11]. In this case, the diagnosis of APS-3B was made when Hashimoto's disease and autoimmune gastritis were diagnosed. Given the possibility of other autoimmune gastrointestinal diseases, we suspected PBC despite the patient testing negative for anti-mitochondrial antibodies and remaining asymptomatic. In the presence of autoimmune thyroid disease, APS-3 should be considered alongside other autoimmune diseases. Furthermore, identifying the APS-3 subclass can help narrow the diagnosis to the specific group of autoimmune diseases. The APS-3 subtypes provide a framework for the differential diagnosis of autoimmune diseases.

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