

A rare combination of type 3 autoimmune polyendocrine syndrome (APS-3) or multiple autoimmune syndrome (MAS-3)

Corrado Betterle · Silvia Garelli · Graziella Coco · Patrizia Burra

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Abstract

Context Type 3 autoimmune polyendocrine syndrome (APS-3) is defined by the presence of an autoimmune thyroid disease and another autoimmune illness, excluding Addison's disease; this is a frequent combination.

Case presentation We report the case of a 55 years old female patient with APS-3, with seven clinical or latent autoimmune manifestations. At 49 years of age she was admitted at the General Hospital for leukopenia, weight loss, tremors, anxiety and diarrhea. The personal history revealed ulcerative colitis and, during the last year, episodes of fever with migrant arthralgia and cutaneous lesions. The patient was evaluated for thyroid function and imaging, mielobiopsy, glycaemic control, gastrointestinal and rheumatologic disorders with specific biochemical tests, imaging and endoscopic procedures. We concluded that the patient was affected by APS-3, characterized by the association of Graves' disease, autoimmune leukopenia, latent autoimmune diabetes of the adult (LADA), autoimmune gastritis, ulcerative colitis, Sjögren's and anti-phospholipid syndromes. The patient started low doses of corticosteroid drugs for leukopenia, underwent ¹³¹I therapy for hyperthyroidism and later started substitutive thyroid therapy with L-thyroxine, insulin therapy for LADA,

mesalazine for ulcerative colitis and artificial tears for Sjögren's syndrome.

Conclusions In this article we report a complex case of APS-3, characterized by the association of seven different autoimmune diseases, which required a complex therapeutic strategy.

Keywords Autoimmune polyendocrine syndrome type 3 · Multiple autoimmune syndrome type 3 · Graves' disease · Diabetes mellitus type 1 · Autoimmune gastrointestinal disorders

Introduction

In 1980 Neufeld and Blizzard [1] proposed the classification of the so called autoimmune polyendocrine syndromes (APS) based on clinical criteria and four main types of APS (type 1, type 2, type 3, type 4) were identified (Table 1).

As regard APS type 3 (APS-3), the same authors subdivided it in three subgroups, based on the association of one thyroid autoimmune disease (TAD) (Hashimoto's thyroiditis, Graves' disease, endocrine ophthalmopathy or pretibial myxoedema) with one or more of the following diseases: diabetes mellitus type 1 (DM-1) (3A), chronic atrophic gastritis or pernicious anemia (3B), and vitiligo, alopecia or myasthenia gravis (3C).

In the course of the subsequent 40 years the number of autoimmune diseases has greatly increased, and on the book published on the occasion of the 50th anniversary from the discovery of autoimmune diseases, about 80 diseases were included [2]. For these reasons we revised and expanded the classification of APS-3 into four subgroups, practically including all autoimmune diseases

G. Coco prematurely dead on 2009 at 31 years of age.

C. Betterle (✉) · S. Garelli · G. Coco
Endocrine Unit, Department of Medicine, University of Padova,
Via Ospedale Civile 105, 35100 Padova, Italy
e-mail: corrado.betterle@unipd.it

P. Burra
Gastroenterology Unit, Department of Surgery, Oncology and
Gastroenterology, University of Padova, Via Giustiniani 2,
35100 Padova, Italy

Table 1 Classification of autoimmune polyendocrine syndromes (APS) modified from Neufeld [1]

APS-1 or APECED (autoimmune-poly-endocrine-candidiasis-ectodermal-dystrophy)	Chronic mucocutaneous candidiasis Chronic hypoparathyroidism Addison's disease (at least two out of three)
APS-2 or Schmidt's syndrome	Addison's diseases + thyroid autoimmune disease and/or diabetes mellitus type 1
APS-3 (excluding Addison's disease)	Thyroid autoimmune disease + DM-1: Type 3A Chronic atrophic gastritis or pernicious anemia: Type 3B Vitiligo, alopecia or myasthenia gravis: Type 3C
APS-4	Any other possible association of autoimmune diseases

associated to TADs (with the exception of AD) (Table 2) [3].

Subsequently some authors proposed a simpler classification in APS type 1 and type 2, because of similar genetic background and pathophysiology between APS type 2, type 3 and type 4. In 2004 Eisenbarth et al. [4] defined the two parties as “splitters” and “lampers”, being in favour of a simpler classification. In our opinion, the classification proposed by Neufeld and Blizzard and completed by us [1, 3] is more practical from a clinical and methodological point of view.

Table 2 The combinations of different autoimmune diseases present in our patient (in italics), with other possible diseases present in a patient with APS/MAS-3

Autoimmune thyroid diseases: <i>Graves' disease</i> , Hashimoto's thyroiditis, endocrine ophthalmopathy, pretibial myxoedema			
<i>Type 1 DM (LADA)</i>	<i>Chronic atrophic gastritis</i> <i>Ulcerative colitis</i>	<i>Autoimmune leukopenia</i>	<i>Sjögren's syndrome</i> <i>Anti-phospholipid syndrome</i>
Hirata's syndrome	Pernicious anemia	Vitiligo	Systemic lupus erythematoses
Premature ovarian failure	Celiac disease	Alopecia	Discoid lupus erythematoses
Adeno-hypophysitis	Other inflammatory bowel diseases	Bullous Skin diseases	Rheumatoid arthritis
Neuro-hypophysitis	Primary biliary cirrhosis	Chronic idiopathic urticaria	Mixed connective tissue disease
Chronic hypoparathyroidism	Autoimmune hepatitis	Myasthenia gravis	Seronegative arthritis
	Sclerosing cholangitis	Stiff-person syndrome	Systemic sclerosis
	Autoimmune pancreatitis	Multiple sclerosis	Dermato/polymyositis
		Autoimmune anemia	Vasculitis
		Autoimmune thrombocytopenia	
Endocrine glands	Gastrointestinal tract and liver	Skin	Autoimmune rheumatic disorders
		Muscles	Vasculitis
		Nervous system	
		Haematologic system	
3A	3B	3C	3D

APS/MAS-3 autoimmune polyendocrine syndrome/multiple autoimmune syndrome type 3

Furthermore, the term APS is not fully appropriate, because it is often used to indicate not only cases of multiple autoimmune endocrine diseases (such as TADs and DM-1), but also associations between endocrine and non-endocrine autoimmune diseases (such as DM-1 with celiac disease or TADs and gastric autoimmunity), or the associations between non-endocrine autoimmune diseases (for instance vitiligo and myasthenia gravis, or autoimmune hepatitis and Sjögren's syndrome). For these reasons, we recently proposed to substitute or to associate to the term APS the term Multiple Autoimmune Syndromes (MAS), because we consider the last a more appropriate term to denote these autoimmune overlapping conditions [5, 6].

In this article we present a complex case of a patient affected by APS/MAS-3 with Graves' disease and six other different clinical or latent autoimmune diseases.

Case presentation

Our patient is a 55 years old Caucasian woman. The family history revealed chronic thyroiditis with hypothyroidism in the mother and in a sister; an aunt and a cousin were affected by Graves' disease, another relative had diabetes mellitus type 2 and a grandfather had Bürger's disease.

Anamnestically, she referred tonsillectomy at the age of 10 years. At 36 years diagnosis of ulcerative colitis was performed. From 36 years she took mesalazine therapy, which was finally stopped for prolonged remission at 46 years of age.

At 48 years she referred episodes of fever up to 39 °C, migrant arthralgia and cutaneous vasculitic lesions; at that time the patient was taking no drug. Blood tests revealed severe leukopenia (870 WBC/mm³) and anti-nuclear antibodies (ANA) positivity (titer of 1:320 with an homogeneous pattern), whereas extractable nuclear antigen antibodies (ENA) were negative. So, a therapy based on antibiotics and granulocyte stimulating growth factor was started, with good acute clinical response; subsequently, leukopenia was stabilized (2,500 WBC/mm³) with low doses of prednisone. A bone marrow needle aspiration was performed, revealing myeloid hyperplasia with reduced number of mature cells: diagnosis of autoimmune leukopenia was established on the basis of chronic presence of ANA positivity, response to steroid therapy and the exclusion of other possible causes.

At 49 years the patient was admitted to the Gastroenterology Division of Padova General Hospital for weight loss and diarrhea. The clinical examination showed the presence of anxiety, tremors and goiter without ophthalmopathy. Hormonal values showed TSH inhibition with high free T4 and free T3 levels, and positivity to antibodies against thyroperoxidase (TPOAbs), thyroglobulin (TgAbs) and TSH receptor (TRAb). Thyroid Doppler-US scan revealed increased gland volume, inhomogeneous hypoechoic structure and intense hypervascularization; an ^{99m}Tc scintigraphy showed increased uptake, so the diagnosis of Graves' disease was established. The patient had persistent modest leukopenia under low doses of prednisone.

Because of leukopenia anti-thyroid drugs weren't started, and the patient was initially treated with symptomatic drugs, such as beta-blockers, and after few weeks with ¹³¹I-therapy. After few more weeks she developed persistent hypothyroidism and substitutive therapy with L-thyroxine (75 gamma/die) was started, with normalization of the thyroid function.

Furthermore, on this occasion microcytic anemia with hypsideremia and thrombocytopenia (121,000/mm³) were also demonstrated in addition to leukopenia. In the suspect of an autoimmune gastritis, specific blood tests revealed the presence of high titers of gastric parietal cells antibodies (PCA), high levels of both gastrinemia and chromogranine A, with negativity for intrinsic factor autoantibodies and tissue transglutaminase of IgA class.

An esophagogastroduodenoscopy (EGDS) was performed and revealed macroscopic evidence of atrophic body gastritis; histological examination confirmed the presence of body and fundus atrophy with intestinal metaplasia, hyperplasia of the enterochromaffin cells without *Helicobacter pylori* infection, while the duodenal biopsy was negative. These data confirmed the presence of autoimmune gastritis. Oral iron replacement therapy was started.

To further investigate thrombocytopenia, the patient underwent an ultrasound examination of the abdomen, which showed an enlarged spleen (diameter 16 cm) with an homogenous pattern. On this occasion, low titers of anti-cardiolipin antibodies (IgM and IgG classes) and anti-beta2-glycoprotein I (IgM class) were documented. High titers (1/640) of ANA were confirmed with homogeneous pattern, but double strain DNA antibodies (dsDNA Abs) and anti-platelet antibodies were negative.

On this occasion hyperglycemia (6.94 mmol/L) was discovered for the first time, with high levels of HbA1c (59 mmol/mol, 7.5 %). For this reason autoantibodies to endocrine pancreas were investigated: high titers (1/160 U/JDF) of islet-cells antibodies (ICA) and glutamic acid decarboxylase autoantibodies (GADAbs) (12.1 U/mL) were identified, while autoantibodies to second islet antigen (IA2Abs) were negative. On the basis of these data, the diagnosis of latent autoimmune diabetes of the adult (LADA) was performed and low dosage insulin therapy was started. During the subsequent years, the patient reported neurological disturbances, simulating sciatic nerve inflammation, and she was treated with anti-inflammatory drugs with no beneficial effect. Later on, the diagnosis of diabetic neuropathy was performed and alpha-lipoic-acid was started with good symptomatic control after few weeks of therapy.

The patient referred also mouth and eye dryness. A Schirmer's test revealed a diminished tear secretion. Autoantibodies to ENA were confirmed to be negative, but a salivary gland US-scan revealed a typical Sjögren's syndrome pattern. No biopsies of minor salivary glands were performed. A topic treatment with artificial tears was started.

During this hospitalization in Gastroenterology Unit, a colonoscopy was also repeated, and revealed signs of silent pancolitis.

The HLA typing of the patient revealed this pattern: A24(9), 26(10); B44(12), 62(15); Cw7; (Bw4); DRB1* 04, 13; DQA1* 0303/0505; DQB1* 0302/0301.

The patient was followed-up by a team of specialists: endocrinologist, diabetologist, gastroenterologist, rheumatologist and haematologist. During the following years she felt quite good, taking previously mentioned medications.

At 55 years she manifested once again gastrointestinal symptoms with fecal blood loss and consequent severe anemia, therefore she underwent colonoscopy which revealed reactivation of ulcerative colitis, indicating the need to start again with mesalazine. After few weeks of therapy she achieved a complete remission of symptoms.

In the same occasion the patient repeated EGDS. Gastric histology showed mild metaplastic-atrophic gastritis, classified as stage II by OLGA System 2005; *Helicobacter*

pylori was negative. So the histological features confirmed the autoimmune gastritis.

The patient underwent biochemical and hormone assessment, showing stable hemoglobin (12 g/L), with good renal and hepatic function. Positivity of gastric mucosa antibodies was reported, as well as increase of gastrin. Low levels of 25-hydroxy vitamin D3 were detected, so an oral supplementation with cholecalciferol was started.

The patient is still on low dose of steroids, mesalazine, insulin, L-thyroxine.

Discussion

TADs are the most frequent autoimmune diseases in the world population, presenting in the majority of cases as spontaneous hypothyroidism, being present in 4–21 % of females and in 3–16 % of males depending on age; hyperthyroidism is rarer, affecting about 0.5 % of population [7, 8]. Furthermore, autoantibodies directed to thyroid antigens have been described in 11 % of euthyroid subjects [9]. About 15 % of the patients with TADs is affected by another clinical autoimmune disease [10] and another 15 % of those with apparently isolated TADs may result positive if screened for organ and non-organ-specific autoantibodies. So, we may conclude that about 30 % of patients with TADs is affected by a clinical, subclinical or potential APS/MAS-3. For this reason APS/MAS-3 is the most common APS/MAS, being present in about 5 % of the female population and 1.5 % of males [6].

The majority of APS/MAS-3 patients presents TADs associated with only another autoimmune disease, and the most common associations are with chronic atrophic gastritis (39 % of the cases) [11] or with DM-1 (20–30 % of the cases) [12, 13]. To our knowledge, only four patients have been described so far with three or more autoimmune diseases complicating TADs. The first was described in Japan and was affected by Graves' disease with other five autoimmune diseases, i.e. DM-1, alopecia areata, autoimmune neutropenia, Sjögren's syndrome and chronic cutaneous lupus erythematosus [14]. Another patient coming from Greece presented Hashimoto's thyroiditis associated with other three autoimmune diseases: DM-1, atrophic gastritis with pernicious anemia and immunologic thrombocytopenic purpura [15]. The third patient was described by American colleagues with silent thyroiditis and other three autoimmune diseases, i.e. isolated corticotropin deficiency, ulcerative colitis and alopecia universalis [16]. An Italian patient with Down's syndrome was described having TAD (Hashimoto's thyroiditis followed by Graves'

disease) with three other diseases, i.e. arthropathy, DM-1 and celiac disease [17].

Our patient had seven autoimmune manifestations and fulfill all four subgroups of APS/MAS-3, being affected by Graves' disease and LADA (3A), autoimmune gastritis and ulcerative colitis (3B), autoimmune neutropenia (3C), Sjögren's syndrome and anti-phospholipids antibodies with thrombocytopenia (3D) (Table 2). Six diseases were clinically evident and one (anti-phospholipid syndrome) was latent, not having clinical symptoms but only autoantibodies and thrombocytopenia.

The management of our patient needed the intervention and cooperation of many different specialists, from endocrinologist to diabetologist, gastroenterologist, rheumatologist and haematologist. Only a multidisciplinary setting allowed to minimize therapies, controlling different illnesses symptoms and reducing drugs side effects.

In patients with TADs without other clinical autoimmune manifestations, we suggest not to perform a universal autoantibodies screening, but to limit the number of exams depending on the family history of the single patient and on the most common associations (chronic atrophic gastritis, DM-1, Sjögren's syndrome and celiac disease); obviously, clinical suspect is fundamental. In the case of negativity, patients should be re-evaluated every 2 or 3 years. This approach permits to identify the eventual ongoing new autoimmune diseases and, if needed, to precociously treat the patient.

In conclusion, in this paper we described a complex case of APS/MAS-3 with seven different diseases, which required a complex therapeutic strategy taking into account adverse effects of drugs.

Conflict of interest Betterle C, Garelli S and Burra P declare that they have no conflict of interest. Coco G had no conflict of interest.

Animal rights As regards the patient described in the submitted case report "A rare combination of type 3 autoimmune polyendocrine syndrome (APS-3) or multiple autoimmune syndrome (MAS-3)", clinical procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 and 2008.

Informed consent As regards the submitted case report "A rare combination of type 3 autoimmune polyendocrine syndrome (APS-3) or multiple autoimmune syndrome (MAS-3)", written consent has been obtained from the patient.

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