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Type 3 autoimmune polyglandular syndrome with multiple genetic alterations in a young male patient with type 1 diabetes mellitus

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Type 1 diabetes mellitus (T1DM) is one of the most common chronic diseases in young patients. Characteristic circulating, islet-specific pancreatic autoantibodies may be present [against insulin, glutamic acid decarboxylase 65 (GAD65), zinc transporter 8 (ZnT8), 40k fragment of tyrosine phosphatase (IA2)] [1], and they can lead to insulin deficiency. Patients with T1DM can develop other organ-specific autoantibodies, causing autoimmune thyroiditis, coeliac disease, or pernicious anaemia, or patients with the mentioned diseases can often develop autoantibodies characteristic to Hashimoto's thyroiditis [2]. At least 2 organ-specific autoimmune diseases can be part of autoimmune polyendocrine/polyglandular syndromes (APS) (Tab. 1).

Table 1. *Autoimmune polyglandular syndromes*

	Characteristic features	Additional features
APS type 1	Two out of three: chronic mucocutaneous candidiasis, hypoparathyroidism, autoimmune adrenal insufficiency	T1DM, pernicious anaemia, hypothyroidism, ectodermal dysplasia, autoimmune hepatitis, primary hypogonadism, alopecia, malabsorption, vitiligo
APS type 2	Autoimmune adrenal insufficiency, autoimmune thyroid disease and/or T1DM	Vitiligo, autoimmune hepatitis, alopecia, pernicious anaemia, primary hypogonadism
APS type 3	Autoimmune thyroid disease and at least one other organ-specific autoimmune disorder, e.g. T1DM, primary hypogonadism, pernicious anaemia, coeliac disease, vitiligo, alopecia, psoriasis that is not Addison's disease or hypoparathyroidism	

APS — autoimmune polyglandular syndrome; T1DM — type 1 diabetes mellitus

A 32-year-old male patient with diabetes mellitus presented to ambulatory care because of suboptimal blood sugar levels, alleged weight loss, vague low-back pain, and supposed malabsorption. The patient history contained 3 years' history of T1DM, 2 years' history of thyroid disease, and mitral and aortic valve prolapse. The patient's mother had Hashimoto's thyroiditis and myasthenia gravis. On physical examination, the patient was underweight (height 180 cm, weight 52 kg, BMI: 16 kg/m^2). His posture, and long limbs and fingers suggested marfanoid habitus. Antibody levels were high (Tab. 2). Based on low BMI, relatively young age, and islet-specific antibody positivity, we could confirm the diagnosis of T1DM.

Table 2. *Laboratory results*

	Value	Reference range
Anti-GAD	1745 IU/mL	< 10 IU/mL
Anti-ZnT8	17 IU/mL	< 15 IU/mL
ATPO	1196 U/mL	< 5.6 U/mL
Vitamin B12	72 pmol/L	138–652 pmol/L
Homocysteine	100.2 μmol/L	5.4–16 μmol/L

anti-GAD — anti-glutamic acid decarboxylase antibody; anti-ZnT8 — anti-zinc transporter 8 antibody; ATPO — anti-thyroid peroxidase antibody

Laboratory values and sonographic morphology were consistent with a euthyroid Hashimoto's thyroiditis (Fig. 1A).

The laboratory tests performed at admission showed mild, macrocytic anaemia. Vitamin B12 level was below the reference range. Gastroscopy showed type A atrophic gastritis, and histological evaluation revealed severe chronic gastritis with intestinal metaplasia without *H. pylori* infection. Immunological tests

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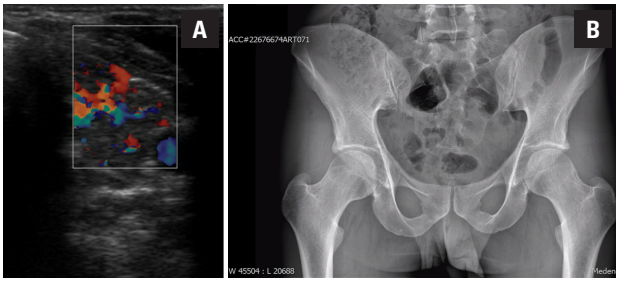

Figure 1A. *Sonographic image of the hypervascularized thyroid gland.* **B.** *There is no clear sign of sacroiliitis on the pelvic X-ray*

were also performed. Anti-parietal cell antibodies tested positive, while antibodies against intrinsic factor were negative. Thus, the diagnosis of pernicious anaemia could be established.

The patient had vitamin B12 malabsorption. However, iron-, lipid-, protein-, and calcium/vitamin D3-metabolism were without marked alterations. Coeliac disease could also be excluded because of the negativity of antibodies against tissue transglutaminase and deamidated gliadin peptides. Gastroscopy showed no typical signs of coeliac disease in the small intestine. There were no ionic disturbances, the fasting serum cortisol level was within the normal range, and no clinical signs of hypoadrenalism were detected; therefore, we could rule out clinically manifested Addison's disease.

Concurrent Hashimoto's thyroiditis, T1DM, and pernicious anaemia, and the absence of Addison's disease and hypoparathyroidism, suggested the diagnosis of type 3 autoimmune polyendocrine syndrome. Maternal anamnesis of Hashimoto's thyroiditis and myasthenia gravis that could be diagnosed also as APS3, strengthens the diagnosis.

We performed further tests because of the marfanoid habitus and valvular prolapses of the patient. Because of the vague low-back pain and the characteristic phenotype of the patient, we performed tests to evaluate ankylosing spondylitis (AS). There was no clear sign of sacroiliitis on plain pelvic X-ray (Fig. 1B). From the 11 characteristic ankylosing spondylitis symptoms, the patient showed only 1, namely HLA-B27 positivity. According to the relevant guideline, sacroiliitis on MRI would further strengthen the diagnosis, but it is itself not diagnostic. Because of vitamin B12 deficiency, the patient's homocysteine level was measured and was found to be extremely elevated. B12 and folate-dependent enzymatic conversions are responsible for keeping homocysteine levels relatively low by conversion to methionine or cysteine. We therefore performed genetic analysis of the 2 most frequent mutations of the methylenetetrahydrofolate reductase (MTHFR) gene. We found the A1298C mutation in homozygous variant [*MTHFR* (methylenetetrahydrofolate reductase) C677T normal variant, *MTHFR* A1298C homozygous variant)]. Therefore, we concluded that the elevated homocysteine level may be explained by vitamin B12 deficiency and the patient's genetic predisposition.

The young patient has type 3 APS. The cardiovascular risk of the patient is higher because of the T1DM. Elevated homocysteine levels are associated with higher cardiovascular risk and more frequent thromboembolic events; moreover, homocysteine is an independent risk factor of cardiovascular diseases [3]. Approximately 10% of the US population are homozygous for the thermolabile variant of *MTHFR* (C677T), and 30% are heterozygous for another polymorphism of *MTHFR* gene; A1298C is found in approximately 10% of the Caucasian population [4]. There is no clear consensus on whether reducing the homocysteine level through vitamin B12 replacement lowers the cardiovascular risk [5]. We observed genetic alteration independent of the comorbidities of type 1 diabetes mellitus.

In conclusion, in patients with type 1 diabetes mellitus and with autoimmune polyglandular syndrome, who have higher cardiovascular risk, the presence of other genetically known risk factors, such as hyperhomocysteinaemia or spondylarthritis, should be considered, in order to initiate preventive measures.

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