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A case of autoimmune urticaria accompanying autoimmune polyglandular syndrome type III associated with Hashimoto's disease, type 1 diabetes mellitus, and vitiligo

Przypadek pokrzywki autoimmunologicznej współistniejącej z autoimmunologicznym zespołem wielogruczołowym typu III związanym z chorobą Hashimoto, cukrzycą typu 1 i bielactwem

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Abstract

We present a case of autoimmune polyglandular syndrome type III (APS III) associated with Hashimoto's disease, type 1 diabetes mellitus, vitiligo and autoimmune urticaria. This rare genetic disorder occurs with unknown frequency in the Polish population. It is characterised by endocrine tissue destruction resulting in the malfunction of multiple organs.

Several cases of APS III associated with organ-specific autoimmune diseases such as coeliac disease, hypogonadism and myasthenia gravis, as well as organ-nonspecific or systemic autoimmune diseases such as sarcoidosis, Sjögren syndrome, and rheumatoid arthritis have been described. To the best of our knowledge, we here describe the first case of APS III associated with autoimmune thyroiditis, type 1 diabetes mellitus, vitiligo and autoimmune urticaria in an adult patient. **(Endokrynol Pol 2014; 65 (4): 320–323)**

Key words: *polyglandular autoimmune syndrome type III; type 1 diabetes mellitus; autoimmune thyroiditis; vitiligo; autoimmune urticaria*

Streszczenie

W pracy przedstawiono przypadek autoimmunologicznego zespołu wielogruczołowego typu III współistniejącego z przewlekłą pokrzywka autoimmunologiczną. Autoimmunologiczny zespół wielogruczołowy jest rzadko rozpoznawany, a częstość jego występowania w Polsce pozostaje nieznana.

Opisano przypadki autoimmunologicznego zespołu wielogruczołowego typu III współistniejącego z innymi chorobami o podłożu autoimmunologicznym, takimi jak choroba trzewna, hypogonadyzm, *miastenia gravis*, jak również z sarkoidozą, zespołem Sjögrena i reumatoidalnym zapaleniem stawów. Nie opisywano jednak wcześniej przypadku współistnienia pokrzywki autoimmunologicznej z autoimmunologicznym zespołem wielogruczołowym typu III. **(Endokrynol Pol 2014; 65 (4): 320–323)**

Słowa kluczowe: *autoimmunologiczny zespół wielogruczołowy typu III; cukrzyca typu 1; autoimmunologiczne zapalenie tarczycy; bielactwo; pokrzywka autoimmunologiczna*

Introduction

Polyglandular autoimmune syndromes (APSs) are a group of autoimmune disorders characterised by endocrine tissue destruction causing malfunction of multiple glands [1]. The first classification of polyglandular failure, distinguishing three types, was developed in 1980 by Neufeld and Blizzard [2]. APS I is characterised by candidiasis of the skin and mucous membranes, hypoparathyroidism and adrenal insufficiency. APS II is composed of adrenal insufficiency, autoimmune thyroid disease and type 1 diabetes mellitus (T1DM).

APS III is a an adult type of APS, characterised by the association of endocrine and non-endocrine organ specific autoimmune disorders [1, 3]. Autoimmune thyroiditis and the absence of adrenal insufficiency are crucial for the diagnosis of all subtypes of APS III [1]. In APS III, autoimmune thyroiditis occurs together with another organ-specific autoimmune disease. APS III can be further divided into three subtypes: APS IIIA — autoimmune thyroiditis AITD with T1DM; APS IIIB — autoimmune thyroiditis with pernicious anaemia; and APS IIIC — autoimmune thyroiditis with vitiligo and/or alopecia and/or another organ-specific autoimmune disease. APS III may be accompanied by other organ-specific autoimmune diseases such as coeliac disease, hypogonadism, myasthenia gravis, autoimmune hepatitis as well as organ-nonspecific or systemic autoimmune diseases like sarcoidosis, Sjogren syndrome, rheumatoid arthritis, autoimmune leucope-

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nia and other diseases such as gastric carcinoid tumour, malabsorption due to exocrine pancreatic deficiency, idiopathic thrombocytopenic purpura or acquired von Willebrand syndrome [1, 3–6]. Amerio et al. considered chronic urticaria as an element of APS III C, however to the best of our knowledge, we here present the first case of APS III associated with autoimmune urticaria [7].

Case report

An obese 37-year-old woman was admitted to the Department of Internal Diseases, Diabetology, and Clinical Pharmacology of the Medical University of Lodz due to weakness, sweating, dyspnoea, and tachycardia. The patient complained of menorrhagia. She had been diagnosed with type 1 diabetes mellitus at the age of 12. Since the diagnosis she had been treated with intensive insulin therapy, and the diabetes was relatively well controlled. At the age of 30, her first vitiligo lesions appeared. Soon after, Hashimoto's disease was diagnosed and treatment with L-thyroxin at a dose of 50 μg/day was started. For several years, she was on antihypertensive medications. Additionally, she had suffered from depression since early adulthood. Several months before the first hospitalisation in our clinic, she was hospitalised due to stroke with paralysis of the left side. Computerised tomography revealed malformation of brain arteries, but the patient did not agree to any further diagnostic or therapeutic procedures. The patient had no family history of APS or autoimmune thyroid disease (AITD) or any other immunological disorders.

The physical examination on admission showed a markedly obese (BMI 38 kg/m^2) woman with visible oedema of the face and extremities. The patient presented with a generalised form of vitiligo. Numerous amelanotic patches were present on the hands, forearms, feet, face and trunk. Neurological examination revealed the signs of distal symmetric polyneuropathy. Signs of hypertonic as well as diabetic retinopathy were seen on ophthalmoscopic examination. ECG tracings showed sinus rhythm 80/min with single supraventricular extrasystoles, and negative T wave in V1-V3 leads. Abdominal ultrasound, as well as chest X-ray, were normal. Thyroid ultrasound revealed small thyroid gland, typically located, without any focal abnormalities. Results of laboratory tests are presented in Table I.

Based on the obtained results, APS III and L-thyroxin overdosing were diagnosed. The dose of L-thyroxin was reduced by 50% and the patient's condition improved two weeks after discharge.

The patient was admitted again to our clinic two years after the first admission due to generalised wheals, redness and itching of the face, trunk and extremities. The skin lesions had appeared several weeks before the hospitalisation. In outpatient settings, she was treated with clemastine (1 mg bid, with a further increase in the dose to 2 mg bid). The clemastine was withdrawn due to side effects, and desloratine (10 mg qd) was administered. Additionally, she was given predisone (60 mg/day, with a further reduction in the dose). Despite treatment with high doses of H_1 antihistamine medications and oral corticosteroids, the skin lesions were resistant to treatment.

During hospitalisation, a differential diagnosis aimed at parasitic infection, *Helicobacter pylori* infection, allergic contact dermatitis, drug eruptions, neoplasia,

Table I. ***Results of basic laboratory tests and diagnostic tests aimed at diagnosis of autoimmune diseases at first admission***

Tabela I. ***Wyniki podstawowych badań laboratoryjnych i badań diagnostycznych mających na celu diagnozowanie chorób autoimmunologicznych podczas pierwszego przyjęcia***

Parameter	Result
Leukocyte count [$10^3/\mu$L]	11.12/9.27
Erythrocyte count [$10^6/\mu$L]	4.44/4.67
Haemoglobin [g/dL]	10.5/10.9
Hematocrit (%)	30.9/33.0
Platelet count [$10^3/\mu$L]	246/303
Iron [μmol/L]	7.05
Total Iron Binding Capacity (TIBC) [mmol/L]	69.9
Unsaturated Iron Binding Capacity (UIBC) [mmol/L]	62.8
Ferritine [ng/mL]	7.57
Alanine aminotransferase (ALT) [U/L]	27
Aspartate aminotransferase (AST) [U/L]	26
Bilirubin [μmol/L]	9.8
Creatinine [μmol/L]	58
Urea [mmol/L]	3.9
Sodium [mmol/L]	138
Potassium [mmol/L]	4.6
Glycated haemoglobin (%)	9.24
Total cholesterol [mmol/L]	5.7
LDL cholesterol [mmol/L]	3.7
HDL cholesterol [mmol/L]	1.11
Triglycerides [mmol/L]	1.78
Thyrotropin (TSH) [μIU/mL]	6.01
Free triiodothyronine (fT3) [pmol/L]	4.76
Anti-thyroid peroxidase antibody Anti-TPO (normal range < 40 UI/mL)	5,917.8
Anti-thyroglobulin antibody Anti-Tg (normal range < 40 UI/mL)	366.17
Anti-thyrotropin receptor antibody TSHR (normal range < 1.5 UI/mL)	13.23
Cortisol (normal range 5–25 μg/dL)	12.9
Adrenocorticotropic hormone (normal range 10–80 ng/L)	16.4

lymphoedema, dermatomyositis, erythema multiforme, and Crohn's disease was performed, and these conditions were excluded. Additionally, the presence of potential foci of inflammation was also excluded.

The suspicion of autoimmune urticaria was made and the patient was consulted in the Clinic of Dermatology and Venerology of the Medical University of Lodz. Implementation of an autologous serum skin test and a skin biopsy were advised, but the patient did not agree to skin biopsy. The results of the autologous serum skin test [8] were positive and a diagnosis of autoimmune urticaria associated with APS III syndrome was made. Oral corticosteroids were initially increased. The patient was highly intolerant to corticosteroids due to substantial weight gain and deregulation of glucose metabolism, and the therapy was withdrawn. Small doses of azathioprine (25 mg qd) were introduced, and the skin lesions disappeared completely within two weeks. After several weeks, the generalised wheals, redness and itching reappeared despite immunosuppressive treatment. The doses of azathioprine were increased, but the efficacy was moderate. The patient herself decided to withdraw immunosuppressive therapy and independently started on a low calorie diet. She was highly motivated and managed to lose 20 kilograms in six months. Symptoms of urticaria subsided gradually with time and disappeared completely within a few months with no treatment. This observation is in agreement with the results of the study of Ye et al., who noted that in a Korean population, the presence of metabolic syndrome was an independent predictor of uncontrolled chronic urticaria [9]. Weight loss also resulted in a substantial improvement of glucose homeostasis and diminishment of symptoms of depression.

Discussion

There are several hypotheses explaining the development of different components of APS III [1, 10–16]. The most widely accepted is the autoimmune genetic hypothesis, assuming involvement of genes associated with immune regulation [17]. Numerous observations have confirmed that genetic susceptibility is shared among autoimmune diseases, with the strongest association seen between T1DM and autoimmune thyroid disease (AITD) [11, 12, 18–21].

The prevalence of APS III in different populations including the Polish population is not known. APS III can occur in persons of any age, although it is most common in middle aged women. The clinical symptoms of individual components of APS III are identical to those of the insufficiency of the individual gland(s). Various skin pathologies related to numerous endocrine disorders, including diabetes mellitus and autoimmune thyroid disease, are relatively common. However, to the best of our knowledge, autoimmune urticaria accompanying APS III syndrome in an adult patient has never been described before.

Chronic urticaria may be associated with autoimmune thyroiditis and antithyroid antibodies [13]. It is supposed to be caused by IgG antibody to the α subunit of the IgE receptor. It seems that activation of complement is associated with augmented histamine secretion by release of C5a [24]. The incidence of anti-thyroid antibodies in chronic urticaria varies between 15% and 24% [25, 26]. Grattan et al. examined antibodies reactive with skin mast cells by performing an autologous skin test. The reaction was positive in 30% of patients with chronic urticaria [27, 28]. In healthy control subjects, or patients with other forms of urticaria, positive reactions were rare. Histological examination in patients with chronic autoimmune urticaria reveals a perivascular infiltrate with $CD4^+$ lymphocytes as well as monocytes, neutrophils, eosinophils, and basophils [24]. As seen in our patient, in the most severe cases of autoimmune urticaria, patients may require treatment with immunosuppressive agent(s).

It is of interest that the symptoms of autoimmune urticaria in the patient subsided gradually with weight loss without any treatment of urticaria. Weight reduction was associated with a substantial improvement in the patient's mood.

In order to unify the obesity with different components of APS III, it is necessary to identify common pathophysiological mechanisms responsible for the metabolic abnormalities at many different levels [29]. Adipose tissue is a hormonally active organ synthesising and secreting a number of very active biomolecules, including adipokines [30–33]. Adipokines are involved in regulating numerous physiologic and pathologic processes through signalling to different organs including the brain, liver and skeletal muscle. Adipokines are also involved in maintaining homeostasis of the immune system, blood pressure, glucose and lipid metabolism as well as pathological processes such as inflammation and atherosclerosis. We did not assess levels of individual adipokines, however one can speculate that weight loss in the described patient had a beneficial impact on the biological activity of adipose tissue. As a consequence, production and secretion of proinflammatory cytokines could be reduced, leading to the diminution of intensity of symptoms of urticaria over time.

Conclusions

Autoimmune urticaria may be associated with autoimmune polyglandular syndrome type III and obesity. It seems that weight reduction could diminish the signs and symptoms of urticaria.

The patient's written consent to the publication of all medical data was obtained prior to submitting this article.

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