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Multiple autoimmune syndrome: type 1 diabetes mellitus, Hashimoto's thyroiditis, systemic lupus erythematosus, rheumatoid arthritis and celiac disease

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Abstract. *Autoimmunity involves a misdirection of the body's immune system against its own tissues, causing a large number of diseases. Various autoimmune disorders are associated with each other but it is very rare to see multiple autoimmune diseases in one patient. Multiple autoimmune syndrome (MAS) is a condition characterized by 3 or more autoimmune disorders in the same individual. Familial, immunologic and infectious factors are implicated in the development of MAS. Here we report a case of co-existence of five autoimmune diseases in a 33-year-old woman, namely type 1 diabetes mellitus, autoimmune hypothyroidism, systemic lupus erythematosus, rheumatoid arthritis and celiac disease which leads to the final diagnosis of multiple autoimmune syndrome type 3 with celiac disease. Patients with a single autoimmune disorder are at 25% risk of developing other autoimmune disorders. The present case draws clinicians' attention to the need for continued surveillance for the development of new autoimmune disease in predisposed patients. The possibility of 3 or more autoimmune disorders occurring in the same patient cannot be fortuitous and suggests a pathogenic relationship between each of them. Presence of an autoimmune disease should elicit vigilance for another one. Occurrence of multiple autoimmune phenomena indicates the need for continued surveillance for the development of new autoimmune disease in predisposed patients. Early identification of the individual disease of MAS is needed in order to decrease the morbidity and mortality associated with MAS. Our case report is of interest because of the rare association of 5 autoimmune disorders. These autoimmune diseases in the described case led to diagnosis of multiple autoimmune syndrome type 3 with celiac disease. Moreover, this case of MAS highlights the importance of a good clinical surveillance in patients with one autoimmune disorder because they have a higher risk of developing another autoimmune disease, even rarely associated with the first one.*

Keywords: *multiple autoimmune syndrome; type 1 diabetes mellitus; Hashimoto's thyroiditis; systemic lupus erythematosus; rheumatoid arthritis; celiac disease*

Introduction

Autoimmune diseases are the conditions initiated by the loss of immunological tolerance to self-antigens, it is a heterogeneous group of disorders in which multiple alterations in the immune system result in a group of syndromes that either target specific organs or affect the body systematically [1].

Multiple autoimmune syndrome (MAS) is defined as occurrence of at least three autoimmune diseases in the same patient [2]. It is further classified into type 1, type 2 and type 3 MAS. The exact pathogenesis of multiple autoimmune syndrome is not known but environmental triggers in genetically susceptible individuals are believed to cause the disorder of immune regulation [2].

Celiac disease affects 1 % of the general population and is an important autoimmune disease, but it is not included in the classification of MAS. As per literature evidence, celiac disease is strongly associated with autoimmune hypothyroidism and type 1 diabetes mellitus in 2–7 and 0.6–16 % of cases, respectively [3, 4], and is very less commonly associated with systemic lupus erythematosus (SLE)

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or rheumatoid arthritis. It is of interest that the presence of one autoimmune disorder makes a path to discover the other autoimmune conditions and improve therapeutic measures. The presented case shows clinicians that there is a need for continuous surveillance for the development of other autoimmune diseases in predisposed patients already diagnosed with autoimmune disease.

Case report

The 33-year-old female patient was referred to our hospital with complaints about fatigue, cough, dyspnea on exertion, intermittent pain in multiple symmetric joints accompanied by morning stiffness which involved small joints of hands, wrists and knees. However, there was no history of any joint swelling. The patient also complained about increased sensitivity to cold and polyuria, polydipsia for the past 3 weeks.

The patient had been diagnosed with type 1 diabetes mellitus (DM) in 2012 and has been treated with insulin (insulin aspart 8–10–8 IU and insulin glargine 28 IU). Her mother refers that sometimes she refuses to do the injections of insulin and does not follow correctly the insulin regimen and the diabetic diet as recommended.

In 2016, she was diagnosed with systemic lupus erythematosus and rheumatoid arthritis. The patient refers that she has been strictly followed up by rheumatologist all this years and received therapy with low doses of oral corticosteroids, practically all the time.

Also there was a history of loose stools on and off since 2 years.

She had irregular menstrual cycles with history of menorrhagia or dysmenorrhea for the last 3 months. Family history is not significant.

On general physical examination, the patient was moderately built, conscious and oriented to time, place and person. Vital signs were within the normal limits.

She was pale and had no icterus, cyanosis, clubbing, koilonychia, lymphadenopathy or pedal edema. There was no swelling in the anterior aspect of neck. She had mild pain on movement of wrist and knee joint; however, there was no joint edema, deformity or restriction of mobility.

Clinical examinations of respiratory, abdominal, and nervous system were unremarkable.

Complete hemogram revealed hemoglobin of 9.3 g% with microcytic hypochromic picture. White blood count and platelet count was normal. Blood glucose and triglycerides were high — 425 and 298 mg/dl, respectively. Cholesterol level was within the normal range.

Renal and liver function tests, serum proteins, serum electrolytes and blood coagulation tests were normal. HIV, HbsAg, HCV antibody tests were non-reactive. The antinuclear antibody (ANA), anti-dsDNA, and rheumatoid factor tests were positive. Fecal occult blood test was negative. Urine complete examination showed albuminuria with urinary protein of 0.35 g/24 h, and there were no dysmorphic red blood cells, leukocytes, or any urinary casts.

The electrocardiographic recording showed sinus rhythm with no significant abnormalities.

2D echocardiography revealed moderate mitral regurgitation, and a high pulmonary artery systolic pressure of 75 mmHg. Considering the heart ultrasound and the clinical examination results we diagnosed moderate mitral insufficiency, heart failure NYHA class II, severe pulmonary hypertension.

Chest X-ray showed no abnormalities.

Thyroid testing demonstrated increased thyroid-stimulating hormone with low free T_3 and free T_4. Both serum thyroglobulin and antiperoxidase antibody tests were positive.

Thyroid ultrasound showed bilateral lobes altered echotexture, with the presence of hypoechoic micronodules, surrounding echoic septations, and decreased flow on color Doppler.

Table 1. Special laboratory investigations

Investigations	Results	Normal range
Fasting blood sugar, mg/dl	288	70–110
2 h after meal blood sugar, mg/dl	402	140–180
HbA1c, %	9.2	4.5–6.3
Thyroid-stimulating hormone, μIU/ml	67.2	2–4.4
Free T_3, ng/dl	0.91	0.60–1.81
Free T_4, ng/dl	0.45	0.93–1.71
Anti-thyroperoxidase antibody, IU/l	2,004	< 35
Thyroglobulin antibody, IU/l	58	< 18
Blood urea nitrogen, mg/dl	40	10–50
Creatinine, mg/dl	1	0.6–1.2
Total protein, g/dl	6.5	6.2–8.4
Albuminemia, g/dl	3.7	3.5–5
Aspartate aminotransferase, U/L	25	0–49
Alanine aminotransferase, U/L	17	0–46
Total bilirubin, mg/dl	0.8	< 1.3
C-reactive protein, mg/dl	11	< 10
Fibrinogen, mg/dl	669	200–400
Cholesterol, mg/dl	189	140–200
Triglycerides, mg/dl	298	50–150
Troponine, pg/ml	0.4	0.12–0.6
Tissue transglutaminase IgA antibody, IU/ml	200	< 20
ANA (indirect immunofluorescence assay) positive, 1 : 980, speckled pattern		
Anti-dsDNA antibody, AI	1.59	< 0.9
Anti-Ro (SS-A) antibody, IU/ml	1.99	< 3
Anti-La (SS-B) antibody, IU/ml	2.76	< 3
Complement component 3, mg/dl	29.5	90–180
Complement component 4, mg/dl	1.87	10–40
Rheumatoid factor, IU/ml	113	1–20
Erythrocyte sedimentation rate, mm/h	37	0–20

These results confirmed the diagnosis of Hashimoto's thyroiditis.

Abdominal ultrasound showed small calculi in the right kidney.

Dual-energy X-ray absorptiometry revealed bone density less than expected for this age group.

Results of fundus oculi examination and electroretinography were normal.

All other laboratory investigations are summarized in Table 1.

In view of tissue transglutaminase IgA positivity and chronic diarrhea, upper gastrointestinal endoscopy was done and biopsy was taken. The results were as follows: increased intraepithelial lymphocytes and lamina propria, inflammatory infiltrate comprising lymphocytes, plasma cells and eosinophils; findings suggestive of celiac disease.

The history, clinical findings and aforementioned laboratory investigations indicated the co-existence of type 1 diabetes mellitus, Hashimoto's thyroiditis, celiac disease, systemic lupus erythematosus (SLICC Revised Criteria) and rheumatoid arthritis.

Thus, the diagnosis was made: MAS type 3 with celiac disease. The patient continued with insulin therapy, levothyroxine, short course of steroids, cardiac medications, and was put on gluten free diet.

She improved gradually and is under regular follow up.

Discussion

All autoimmune disorders are developed only in persons who have genetic predisposition. Genetic basis is represented by HLA antigens, or mutant genes. On the other hand, immune response genes are neighbors with major histocompatibility complex. This complex codes for HLA antigens. Immune response genes and major histocompatibility complex are on the short arm of chromosome 6.

Multiple autoimmune syndrome is a condition with co-existence of 3 or more autoimmune disease in a single patient.

It is further classified into MAS type 1, 2 and 3 as described in Table 2. This classification is important in detecting a new disease entity which can appear in a patient who has had prior autoimmune diseases. It gives a basis for analysis of the pathophysiology of autoimmunity.

The pathogenesis of multiple autoimmune disorders is not clearly understood but certain environmental factors are believed to cause disorders of immune regulation in genetically predisposed individuals. Multiple autoantibodies can be found in a patient, and some of the specific mono- or polyclonal autoantibodies may be multiple organ-reactive. Researchers note that in many cases, the presence of one autoimmune disorder leads to discovery of other autoimmune conditions.

It has been evidenced that the development of type 1 DM increases the risk of other autoimmune diseases. This is related to genetic predisposition to the development of these diseases. The autoimmune process progressing in pancreatic beta cells can also affect other organs, resulting in the development of organ-specific autoimmune diseases, or pathologies of various nonspecific tissues and organs, leading to the development of organ-nonspecific autoimmune diseases [5].

The most frequent comorbidities of type 1 DM include Hashimoto's thyroiditis (autoimmune thyroid diseases) and celiac disease. The frequency of these diseases is increased in patients with type 1 DM as compared to healthy children and adolescents [6, 7]. The occurrence of other autoimmune diseases in patients with type 1 DM deteriorates the quality of life and increases morbidity and mortality [8, 9].

In our patient with type 1 DM, other autoimmune disease was diagnosed based on symptoms: fatigue, increased sensitivity to cold, low thyroid hormones, high level of thyroid-stimulating hormone, positive thyroid peroxidase antibody and thyroglobulin antibody tests, hypoechoic micronodules on ultrasound. These results confirmed the diagnosis of Hashimoto's thyroiditis. Considering that the patient has heart failure as a complication of her rheumatologic disorders, we recommended starting the treatment with low doses (25 μg/day) of levothyroxine.

The patient was tissue transglutaminase IgA positive and her duodenal biopsy was suggestive of celiac disease. Evidence shows that in patients with celiac disease, occurrence of thyroid dysfunction is up to 10 % of cases, and risk of thyroid disease is threefold higher. The co-existence of autoimmune thyroid disease and celiac disease is thought to be due to a common genetic predisposition. Inheritance of HLA-DQ2 and DQ8 haplotypes which are over-represented in many autoimmune diseases and associated with immunological phenotype may explain the link [10].

Considering that Sjögren's syndrome is autoimmune disease that usually co-exists with autoimmune thyroiditis,

Table 2. Types of multiple autoimmune syndrome

Type 1	Type 2	Type 3
Myasthenia gravis	Sjögren's syndrome	Sjögren's syndrome
Thymoma	Systemic lupus erythematosus	Myasthenia gravis and/or thymoma
Polymyositis	Rheumatoid arthritis	Addison's disease
Giant cell myocarditis	Primary biliary cirrhosis	Type 1 diabetes mellitus
	Scleroderma	Autoimmune hemolytic anemia, pernicious anemia, idiopathic thrombocytopenic purpura
	Autoimmune hypothyroidism	Autoimmune hypothyroidism
		Dermatitis herpetiformis

SLE and arthritis, we suspected this diagnosis. Sjögren's syndrome is 10 times more frequent in patients with autoimmune thyroid disease and SLE. But our patient had not symptoms suggestive of Sjögren's syndrome which was later excluded by negative Schirmer's test, anti-Ro and anti-La antibodies.

The patient had features of SLE (small oral ulcers, synovitis, photosensitivity, proteinuria) with presence of ANAs, anti-dsDNA antibodies, and SLICC criteria for classification of SLE were met.

Approximately 15–30 % of patients with SLE have antithyroid antibodies while 6 % had actual hypothyroidism. There are reports of patients with SLE having the antigliadin autoantibodies but no evidence of celiac disease on biopsy [11, 12].

Approximately 30 % of patients with SLE develop another autoimmune condition [13]. It is very rare to see the co-existence of SLE and rheumatoid arthritis.

Type 1 DM raises the risk of having rheumatoid arthritis by 20 % but it rarely co-exists with SLE, though few patients have been reported to have both DM and SLE [14]. S.K. Kota et al. studied the co-existing autoimmune conditions in patients with type 1 DM [15]. Three of 260 patients (1.2 %) had concomitant SLE [10]. S. Cortes et al., on the other hand, examined lupus cohort and identified diabetic patients [16]. Three of 485 individuals had type 1 DM (0.61 %) and six had type 2 DM (0.82 %) [16], further proving the rarity of this co-existence.

In conclusion, our case report is of interest because of the rare association of 5 autoimmune disorders. These diseases in described patient lead to the diagnosis of multiple autoimmune syndrome type 3 with celiac disease.

Moreover, this case of MAS necessitates the importance of a good clinical surveillance in patients with one autoimmune disorder because they have a higher risk of developing another autoimmune disease, even rarely associated with the first one.

Conclusions

Patients with a single autoimmune disorder are at 25% risk of developing other autoimmune diseases [10]. The possibility of 3 or more autoimmune diseases occurring in the same patient cannot be fortuitous and suggests a pathogenic relationship between each of them. Presence of an autoimmune disease should elicit vigilance for another one. Occurrence of multiple autoimmune phenomena indicates the need for continued surveillance for the development of new autoimmune disease in predisposed patients. Early identification of the individual disease of the MAS is needed in order to decrease the morbidity and mortality associated with MAS.

Conflicts of interests. Authors declare the absence of any conflicts of interests and their own financial interest that might be construed to influence the results or interpretation of their manuscript.

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Автоімунний полігландулярний синдром: цукровий діабет 1-го типу, тиреоїдит Хашимото, системний червоний вовчак, ревматоїдний артрит і целіакія

Резюме. Автоімунітет передбачає патологічний збій імунної системи організму, спрямований проти власних тканин, що спричиняє велику кількість захворювань. Різні автоімунні розлади пов'язані між собою, але нечасто можна спостерігати декілька автоімунних захворювань в одного пацієнта. Автоімунний полігландулярний синдром (АПС) — це стан, що характеризується трьома або більше автоімунними порушеннями в однієї людини. Сімейні, імунологічні та інфекційні фактори залучені в патогенез АПС. Автори описують клінічний випадок одночасної наявності п'яти автоімунних захворювань у 33-річної жінки, а саме: цукрового діабету 1-го типу, автоімунного гіпотиреозу, системного червоного вовчака, ревматоїдного артриту і целіакії, що обумовило остаточний діагноз: автоімунний полігландулярний синдром 3-го типу з целіакією. Пацієнти з окремим автоімунним розладом мають підвищений на 25 % ризик розвитку інших автоімунних порушень. У цьому випадку клініцисти підкреслюють необхідність постійного спостереження за розвитком нових автоімунних захворювань у схильних до них пацієнтів. Можливість виникнення трьох або більше автоімунних розладів у одного пацієнта не може бути випадковістю і свідчить про патогенетичний зв'язок між кожним із них. Наявність одного автоімунного захворювання вже насторожує стосовно появи іншого. Виникнення автоімунних полігландулярних симптомів свідчить про необхідність постійного спостереження за розвитком нових автоімунних захворювань у схильних до них пацієнтів. Рання ідентифікація окремого випадку АПС необхідна для зниження захворюваності та смертності, пов'язаних з АПС. Описаний клінічний випадок становить інтерес внаслідок рідкісної асоціації відразу 5 автоімунних розладів. Ці автоімунні захворювання в одного пацієнта дозволяють діагностувати автоімунний полігландулярний синдром 3-го типу з целіакією. Більше того, цей випадок АПС підкреслює важливість належного клінічного спостереження за пацієнтами з одним автоімунним розладом, оскільки вони мають більший ризик розвитку іншого автоімунного захворювання.

Ключові слова: автоімунний полігландулярний синдром; цукровий діабет 1-го типу; тиреоїдит Хашимото; системний червоний вовчак; ревматоїдний артрит; целіакія

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Аутоиммунный полигландулярный синдром: сахарный диабет 1-го типа, тиреоидит Хашимото, системная красная волчанка, ревматоидный артрит и целиакия

Резюме. Аутоиммунитет подразумевает патологический сбой иммунной системы организма, направленный против собственных тканей, что вызывает большое количество заболеваний. Различные аутоиммунные расстройства связаны между собой, но редко можно наблюдать несколько аутоиммунных заболеваний у одного пациента. Аутоиммунный полигландулярный синдром (АПС) — это состояние, характеризующееся тремя или более аутоиммунными нарушениями у одного человека. Семейные, иммунологические и инфекционные факторы вовлечены в патогенез АПС. Авторы описывают клинический случай одновременного наличия пяти аутоиммунных заболеваний у 33-летней женщины, а именно: сахарного диабета 1-го типа, аутоиммунного гипотиреоза, системной красной волчанки, ревматоидного артрита и целиакии, что обусловило окончательный диагноз: аутоиммунный полигландулярный синдром 3-го типа с целиакией. Пациенты с одним аутоиммунным расстройством имеют повышенный на 25 % риск развития других аутоиммунных нарушений. В этом случае клиницисты подчеркивают необходимость постоянного наблюдения за развитием новых аутоиммунных заболеваний у предрасположенных к ним пациентов. Возможность возникновения трех или более аутоиммунных нарушений у одного пациента не может быть случайностью и свидетельствует о патогенетической связи между каждым из них. Наличие одного аутоиммунного заболевания уже настораживает относительно появления другого. Возникновение аутоиммунных полигландулярных симптомов свидетельствует о необходимости постоянного наблюдения за развитием новых аутоиммунных заболеваний у предрасположенных к ним пациентов. Ранняя идентификация отдельного случая АПС необходима для снижения заболеваемости и смертности, связанных с АПС. Описанный клинический случай представляет интерес вследствие редкой ассоциации сразу 5 аутоиммунных расстройств. Эти заболевания у одного пациента позволяют диагностировать аутоиммунный полигландулярный синдром 3-го типа с целиакией. Более того, данный случай АПС подчеркивает важность надлежащего клинического наблюдения за пациентами с одним аутоиммунным расстройством, поскольку они имеют больший риск развития другого аутоиммунного заболевания.

Ключевые слова: аутоиммунный полигландулярный синдром; сахарный диабет 1-го типа; тиреоидит Хашимото; системная красная волчанка, ревматоидный артрит; целиакия