

CASE REPORT**A Case of Autoimmune Polyglandular Syndrome Type 2 Associated with Atypical Form of Scleromyxedema****Oleksander Prylutskyi¹, Olga Prylutska¹, Anatoliy Degonskyi¹, Kseniia Tkachenko¹****ABSTRACT**

BACKGROUND: Autoimmune polyglandular syndrome type 2 represents an uncommon endocrine disorder composed by Addison's disease with autoimmune thyroid disease (Schmidt's syndrome) and/or type 1 diabetes mellitus. Scleromyxedema is a rare progressive cutaneous mucinosis usually associated with systemic involvement and paraproteinemia. To the best of our knowledge, there is no case report of Schmidt's syndrome associated with scleromyxedema.

CASE DETAILS: A 34-year-old woman was admitted to Donetsk Clinical Territorial Medical Association due to acute general weakness, reduced vision, dryness of integuments, memory decline, fatigue, weight loss, rash on the face trunk and extremities. A diagnosis of APS type II was made comprising of autoimmune hypothyroidism and autoimmune adrenal insufficiency. Skin histopathologic examination demonstrated the presence of mucin deposits, dermal fibrosis, fibrocytes and perivascular inflammation. In the absence of monoclonal paraproteinemia and the presence of typical histological and clinical signs, an atypical form of scleromyxedema was diagnosed. The patient was administered a lifetime replacement levothyroxine and methylprednisolone therapy.

CONCLUSION: Identification and adequate treatment of both APS type II and scleromyxedema in affected patients pose a problem due to the lack of facilities for diagnosis and management plus common misdiagnosis. Early diagnosis should be made before the development of life-threatening complications.

KEYWORDS: Autoimmune polyglandular syndrome type II, Autoimmune thyroiditis, Addison's disease, Scleromyxedema atypical form

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INTRODUCTION

Autoimmune polyglandular syndrome type 2 represents an uncommon endocrine disorder composed by Addison's disease with autoimmune thyroid disease (Schmidt's syndrome) and/or type 1 diabetes mellitus (1). The prevalence of APS type II is 1:20 000. It is more frequently encountered among women, and the male-to-female ratio is 1:3. This syndrome has a peak incidence at ages 20–60 years, mostly in the third or the fourth decade, and it is common for multiple generations to be affected by one or more component diseases (2). The rarity of the condition and the atypical presentation of adrenal

insufficiency and hypothyroidism often lead to misdiagnosis with life-threatening consequences for the patient (3).

Scleromyxedema is a rare progressive cutaneous mucinosis usually associated with a systemic involvement and paraproteinemia. It was first defined by Arndt and Gottron (1954) (4), then redefined by Rongioletti and Rebora (2001) (5). Scleromyxedema is characterised by a generalised papular and sclerodermoid eruption, monoclonal gammopathy (mostly Ig- λ paraproteinemia) and a triad of histological features: presence of mucin deposition within the upper and mid reticular dermis, fibroblast proliferation and fibrosis with

¹Department of Clinical Immunology, Allergology and Endocrinology, Donetsk National Medical University, Ukraine,

Corresponding Author: Kseniia Tkachenko, Email: t.xeniya@mail.ru

the absence of a thyroid disorder (5,6). It should be noted that there are case reports showing the association of Hashimoto's Thyroiditis and hypothyroidism with scleromyxedema though absence of thyroid disorder is in the diagnostic criteria of scleromyxedema (7,8).

We present a case of autoimmune polyglandular syndrome type 2 in a 34-year-old woman with atypical form of scleromyxedema. This combination of syndromes has not been reported and warrants further investigation.

CASE REPORT

A 34-year-old woman was admitted to the Donetsk Clinical Territorial Medical Association due to acute general weakness, reduced vision, dryness of integuments, memory decline, fatigue, weight loss, rash on the face trunk and extremities. There was neither family history of notable illness, including autoimmune disease, nor allergic background. She noticed papular eruption on the cheeks, wrists and ankles after emotional stress when she was about 24 years old. She was examined by dermatologist, and endocrinologist, lichen myxodermatosus was diagnosed. The decrease of T4 level and one solid nodule in the right thyroid lobe were revealed. Two years later, skin histopathologic examination demonstrated the presence of mucin deposits, dermal fibrosis, fibrocytes and perivascular inflammation. It was noted that such histologic changes were typical for scleromyxedema. She was administered with vitamin B complex and doxycycline (100mg/day) for two weeks. Subsequently, cutaneous manifestations exacerbation was noted. At the age of 28, our patient started with diprosan injections and took glucocorticoids for next 5 years. When she was 33 years old, seven sessions of plasmapheresis were held and she was administered with methylprednisolon (8mg/day). Positive anti-HCV IgG was revealed few months later. Hepatitis C RNA by PCR was found to be positive with a value of 3,200,000 IU/mL. Therefore, she was administered with a course of recombinant human interferon-alpha-2b and stopped taking glucocorticoids. However, the patient developed the fever up to 39,0°C and showed the skin lesions progression, thereby methylprednisolon administration was renewed and interferon-alpha-2b injections was discontinued immediately.

On physical examination upon admission, the general development of the patient was good. The patient's characteristics were the following: temperature, 36,6°C; pulse, 90 beats/min; blood pressure, 100/60 mmHg and respiratory rate 18 breaths/min. She had skin dehydration and induration with flesh-colored papular skin eruption in a linear pattern mainly on the face, neck, upper trunk and hands (Figure 1). The patient exhibited a "doughnut sign," ie, a central depression surrounded by an elevated rim on the metacarpophalangeal joints (Figure 2). Involvement of the ears with papular thickening and deep furrows on the glabella produced a leonine facies (Figure 3). Skin examination also revealed diffuse hyperpigmentation more marked on extensor surfaces (elbows and knees) and intertriginous areas. Reduced articular mobility and difficulty in opening the mouth were present. The patient exhibited nasal tone of voice. The thyroid gland did not enlarge. On cardiovascular and respiratory examinations, no significant signs were detected. The abdomen was soft and not tender with normal bowel sounds; there was tender liver palpable 2 cm below costal margin. There was no splenomegaly. The patient denied incontinence, dysuria, urinary frequency, diarrhea and constipation.



Figure 1: Papular skin eruption in a linear pattern on the upper trunk



Figure 2: "Doughnut sign" on the metacarpophalangeal joint



Figure 3: Leonine facies

From the laboratory work-up, complete blood count, blood sugar, blood urea, serum creatinine, total and direct bilirubin, total protein, lactate dehydrogenase, alkaline phosphatase, creatine kinase, serum iron levels were normal. Serum protein electrophoresis showed albumin fraction of 62,5%, α 1-globulin fraction of 2,5%, α 2-globulin fraction of 9,3%, β -globulin fraction of 11,5% and γ -globulin fraction of 14,2% with the absence of monoclonal component. At the same time, blood biochemistry tests showed significantly elevated alanine aminotransferase

(95,5 IU/ml) and aspartate aminotransferase (66,9 IU/ml) levels.

Inflammation profile studies were unremarkable, with exception of circulating immune complexes (169 U/ml; normal range 40 U/ml to 70 U/ml). Rheumatoid factor, antinuclear factor, cryoglobulins, antibodies against centromere and antibodies against nuclear ribonucleoprotein (anti-RNP-70) values were normal. The patient had normal TTG level (1.4 mIU/l; normal range 0.23 mIU/l to 3.4 mIU/l) low free T4 levels (9.4 pmol/l; normal range 11pmol/l to 26 pmol/l) and low cortisol levels (34 nmol/L; normal range 150nmol/l to 660 nmol/l), which did not rise after cosyntropin stimulation testing. She was also found to have positive anti-thyroid peroxidase and anti-thyroglobulin antibodies. Detection of circulating adrenal cortex autoantibodies confirmed the diagnosis of APS type II syndrome.

Routine urine studies were unremarkable. However, Nechiporenko urine analysis revealed 5700 leukocytes (normal range under 2000) and 1700 erythrocytes (normal range under 1000).

Chest X-ray view presented with diffuse lung fibrosis. Electrocardiogram and 2-dimensional echocardiography did not show any abnormality. Abdominal ultrasonography scan showed a pattern of chronic liver damage. Neither portal vein expansion nor other signs of portal hypertension were described. The diagnosis of urolithiasis disease was confirmed by the presence of hyperechoic formations approximately 2x4 mm in size, occupying both right and left pyelocaliceal kidney systems.

A diagnosis of APS type II was made comprising of autoimmune hypothyroidism and autoimmune adrenal insufficiency. In the absence of monoclonal paraproteinemia, the presence of typical histological and clinical signs, an atypical form of scleromyxedema was diagnosed. Glucocorticoid therapy and intravenous fluid resuscitation quickly increased blood pressure to normal values. The patient was administered a lifetime replacement levothyroxine and methylprednisolone therapy.

DISCUSSION

To the best of our knowledge, there is no case report of Schmidt's syndrome associated with

scleromyxedema. It is considered that scleromyxedema usually occurs in patients with intact thyroid function. At the same time, there are some case reports of scleromyxedema occurring both in hypothyroidism and hyperthyroidism (7,8). In contrast to the preexisting opinion (9), it is highlighted that the presence of thyroid disease could not be an exclusion criterion for scleromyxedema (8). Moreover, our case is an atypical scleromyxedema because the patient had no monoclonal gammopathy. It is important to note that the correct diagnosis requires both typical skin lesions and appropriate biopsy results. Scleromyxedema usually manifests as a generalized symmetric eruption of 2-3 mm firm waxy papules in a linear pattern that converge in indurated plates on the extremities, upper trunk, glabella, neck and ears. Extracutaneous manifestations include cardiovascular, gastrointestinal, pulmonary, rheumatologic and neurologic signs and symptoms. Treatment options are limited, often ineffective and associated with serious life-threatening side effects including bone marrow suppression, irreversible peripheral neuropathy, Cushing's syndrome and osteoporosis etc. (10). Current therapies usually consist of chemotherapy agents such as mephalan and cyclophosphamide, plasmapheresis, retinoids, intravenous immunoglobulins (IVIG), psoralen plus ultraviolet A (PUVA), thalidomide, autologous stem cell transplant and corticosteroids (11).

Scleromyxedema has been associated with many systemic disorders: autoimmune processes including diabetes mellitus and multiple sclerosis, malignancies, lymphoproliferative disorders and a variety of metabolic abnormalities. However, the combination of autoimmune polyglandular syndrome type II (including Schmidt's syndrome) and scleromyxedema have not been described. It has rarely been reported with hepatitis C virus (11-14). The possibility of interferon-alfa treatment in such patients poses a matter of dispute. Taking into account a severe reaction of our patient to interferon-alfa injections, we share the opinion of restricting its administration in patients with scleromyxedema as medicine that may lead to complications (13,14).

It should be noted that, in our case, there was an atypical autoimmune polyglandular syndrome type II initial presentation. In terms of the

sequence of the development of endocrine gland insufficiency in the Schmidt's syndrome, it has been reported that in one half of the cases, autoimmune adrenal insufficiency is the abnormality that occurs first (15) while thyroid failure tends to occur simultaneously or after the emergence of autoimmune Addison's disease (16). Thus, the sequence of the autoimmune gland insufficiency was unusual. Although one out of two patients with autoimmune adrenal insufficiency may develop autoimmune thyroiditis, only one out of 100 of patients with thyroid disease will develop adrenal insufficiency. In order to help optimize patient outcomes, early diagnosis and treatment are critical. Treatment is based on the hormonal replacement of the component endocrinopathies (3).

It is of paramount importance for our patient to have multidisciplinary management including endocrinologist, dermatologist, immunologist, neurologist and psychiatrist according to the high incidence of encephalopathy, psychosis, seizures, memory loss, gait disorders and dysarthria in patients with scleromyxedema. Psychiatric manifestations are also well-documented in Addison's disease (17). In order to provide effective treatment and prophylaxis of Hepatitis C virus, our patient also needs infectologist supervision.

In summary, we described here a case of Schmidt's syndrome associated with atypical form of scleromyxedema. To the best of our knowledge, there is no case report of autoimmune polyglandular syndrome type 2 associated with scleromyxedema. Identification and adequate treatment of both APS type II and scleromyxedema in affected patients pose a problem due to the lack of facilities for diagnosis and management plus common misdiagnosis. Early diagnosis should be made before development of life-threatening complications.

REFERENCES

1. Anyfantakis D, Symvoulakis EK, Vourliotaki I, Kastanakis S. Schmidt's syndrome presenting as a generalised anxiety disorder: a case report. *Journal of Medicine and Life*. 2013;6(4):451-3.
2. Kahaly GJ. Polyglandular autoimmune syndromes. *European Journal of Endocrinology*. 2009;161:11-20.

3. Majeroni PA, Patel P. Autoimmune polyglandular syndrome type II. *Am Fam Physician*. 2007;75:667-77.
4. Brown-Falco O, Burgdorf WHC, Wolff HH, Landthaler M. Dermatology. *Czelej, Lublin*. 2011;1289-90.
5. Rongioletti F, Rebora A. Updated classification of papular mucinosis, lichen myxodermatosus and scleromyxedema. *J Am Acad Dermatol* 2001;44:273-81.
6. Koronowska SK, Osmola-Mańkowska A, Jakubowicz O, Żaba R. Scleromyxedema: a rare disorder and its treatment difficulties. *Postep Derm Alergol* 2013;30(20):122-6.
7. Van Linthoudt D, Schumacher HR Jr, Algeo S, Freundlich B, Schotland DL, Wood MG. Scleromyxedema with myopathy and hyperthyroidism. *J Rheumatol*. 1996;23(7):1299-301.
8. Volpato MB, Jaime TJ, Proença MP, Gripp AC, Alves Mde F. Papular mucinosis associated with hypothyroidism. *An Bras Dermatol*. 2010;85(1):89-92.
9. Pomann JJ. Scleromyxedema revisited. *Int J Dermatol*. 2003;42(1):31-5.
10. Bidier M, Zschoche C, Gholam P, Enk A, Hadashik E. Scleromyxoedema: Clinical follow-up after successful treatment with high-dose immunoglobulins reveals different long-term outcomes. *Acta Derm Venereol*. 2012;92(4):408-9.
11. Altunay I, Erfan G, Gunes P, Serdar Z, Yasar S. Generalized Papular and Sclerodermoid Eruption: Scleromyxedema. *Indian Journal of Dermatology, Venereology and Leprology*. 2010;76(5):592.
12. Smith JA, Kalimullah FA, Erickson CP, Peng LS. Scleromyxedema secondary to hepatitis C virus and successfully treated with antiviral therapy. *Dermatology Online Journal*. 2015;21(9):5.
13. Rongioletti F, Rebora A. Worsening of lichen myxodermatosus during interferon alfa-2a therapy for chronic active hepatitis C. *J Am Acad Dermatol*. 1998;38(5 Pt 1):760-1.
14. Siewert E, Weyers W, Dietrich CG, Geier A, Lammert F, Matern S. Cutaneous mucinosis and skin necrosis complicates interferon alfacon-1 (consensus interferon) treatment of chronic hepatitis C. *Eur J Med Res*. 2005;10(2):63-7.
15. Betterle C, Dal Pra C, Zanchetta R. Autoimmune adrenal insufficiency and autoimmune polyendocrine syndromes: autoantibodies, autoantigens and their applicability in diagnosis and disease prediction. *Endocr Rev*. 2002;23:327-64.
16. Betterle C, Volpato M, Greggio AN, Presotto F. Type 2 polyglandular autoimmune disease (Schmidt's syndrome). *J Pediatr Endocrinol Metab*. 1996;9:113-23.
17. Anglin RE, Rosebush PI, Mazurek MF. The neuropsychiatric profile of Addison's disease: revisiting a forgotten phenomenon. *J Neuropsychiatry Clin Neurosci*. 2006;18:450.