

## Clinical case

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### ANTISYNTHETASE SYNDROME: COURSE OF A RARE DISEASE ON EXAMPLE OF CLINICAL CASE

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Systemic disorders of connective tissue refer to rare and poorly studied diseases. This group of diseases associated with the variable course and makes it interesting for either medical scientists and researchers or practitioner. Herein we report a case of antisynthetase syndrome with interstitial lung disease complicated by pulmonary thromboembolism. The patient is 71 year old female, who suffered from severe dyspnea, dry cough, intermittent wheezing. Also she had dry eyes, dry mouth, muscle weakness and intermittent pain in large joints, and low grade fever. Physical examination revealed a characteristic heliotrope eye rash, V sign, «mechanic's hand», peripheral muscles atrophy, dry eyes and mouth, fine crackles to auscultation in basal parts of lungs, soft S1 and S2 heart sounds. Her biochemical profile showed increased creatinekinase, LDH, AsAT, and ALAT Her immunology results were positive to ANA, anti-ds-DNA, anti-ss-A, anti-ss-B and anti-Jo-1 autoantibodies. Based on the obtained data, antisynthetase syndrome was established. It was detected, that progressive dyspnea had been caused by interstitial lung disease and pulmonary thromboembolism. It was confirmed by chest CT-scan and pulmonary angiography. Treatment in this case is mainly symptomatic. It was prescribed glucocorticoids, immunosuppressant, and anticoagulants. This case illustrates the course of the antisynthetase overlap syndrome and difficulties of it management due to the lack of treatment standards and reliable data of the medicine effectiveness.

**KEY WORDS:** overlap syndrome, antisynthetase syndrome, anti-Jo-1 autoantibodies, interstitial lung disease, pulmonary thromboembolism

### АНТИСИНТЕТАЗНИЙ СИНДРОМ: ПЕРЕБІГ РІДКІСНОГО ЗАХВОРИЮВАННЯ НА ПРИКЛАДІ КЛІНІЧНОГО ВИПАДКУ

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Системні захворювання сполучної тканини відносяться до рідкісних і маловивчених хвороб. Клінічний перебіг даної групи захворювань варіабельний, що і робить їх привабливим об'єктом вивчення як для вчених, так і для практичних лікарів. У даній статті ми опишемо клінічний випадок антисинтетазного синдрому з інтерстиціальним ураженням легень, ускладнений тромбоемболією легеневої артерії. Пацієнт – 71-річна жінка зі скаргами на виражену задишку, сухий кашель, періодичний затруднений видих, що супроводжується свистом. Також у неї були присутні сухість очей і ротової порожнини, м'язова слабкість, періодичні болі в великих суглобах, субфебрильна температура. При об'єктивному огляді звертали на себе увагу характерний періорбітальний геліотропний сип, симптом V – еритема обличчя і шиї, «рука механіка», атрофія периферійних м'язів, сухість очей і порожнини рота, вологі дрібно пухирчасті хрипи в базальних відділах обох легень, глухі тони серця. В біохімічному аналізі крові відзначалося значне підвищення креатинфосфокінази, ЛДГ, АСТ, АЛТ. В імунологічному профілі були позитивні аутоантитіла до ANA, anti-ds-DNA, anti-ss-A, anti-ss-B і anti-Jo-1. На підставі отриманих даних, пацієнтці встановили діагноз антисинтетазний синдром. За допомогою комп'ютерної томографії грудної клітини та ангіографії легень було визначено, що прогресуюча задишка обумовлена інтерстиціальним ураженням легень та тромбоемболією легеневої артерії. Лікування в даному випадку симптоматичне. Пацієнтка отримувала глюкокортикостероїди, імуносупресанти та антикоагулянтну терапію. Даний клінічний випадок

відображає перебіг антісинтетазного синдрому та труднощі в проведенні терапії через відсутність стандартів лікування й достовірних даних про ефективність препаратів.

**КЛЮЧОВІ СЛОВА:** оверлап синдром, антісинтетазний синдром, анти-Jo-1 аутоантітіла, інтерстиціальна хвороба легень, тромбоемболія легеневої артерії

## АНТИСИНТЕАЗНЫЙ СИНДРОМ: ТЕЧЕНИЕ РЕДКОГО ЗАБОЛЕВАНИЯ НА ПРИМЕРЕ КЛИНИЧЕСКОГО СЛУЧАЯ

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Системные заболевания соединительной ткани относятся к редким и малоизученным болезням. Клиническое течение данной группы заболеваний вариабельно, что и делает их привлекательным объектом изучения, как для ученых, так и для практических врачей. В данной статье мы изложим клинический случай антісинтетазного синдрому с інтерстиціальним поражением легких, осложненный тромбоемболией легочной артерии. Пациент – 71-летняя женщина с жалобами на выраженную одышку, сухой кашель, периодический затрудненный выдох сопровождающийся свистом. А также у нее присутствовали сухость глаз и полости рта, мышечная слабость, периодические боли в крупных суставах, субфебрильная температура. При объективном осмотре обращали на себя внимания характерная периорбитальная гелиотропная сыпь, симптом V – эритема лица и шеи, «рука механика», атрофия периферических мышц, сухость глаз и полости рта, мелкопузырчатые влажные хрипы в базальных отделах обеих легких, глухие тона сердца. В биохимическом анализе крови отмечалось значительное повышение креатинфосфокиназы, ЛДГ, АСТ, АЛТ. В иммунологическом профиле были положительные аутоантитела к ANA, anti-ds-DNA, anti-ss-A, anti-ss-B и anti-Jo-1. На основании полученных данных, пациентке был установлен диагноз антісинтетазный синдром. С помощью компьютерной томографии грудной клетки и ангиографии легких было определено, что прогрессирующая одышка обусловлена интерстициальным поражением легких и тромбоемболией легочной артерии. Лечение в данном случае симптоматическое. Пациентка получала глюкокортикостероиды, иммуносупрессанты и антикоагулянтную терапии. Данный клинический случай иллюстрирует течение антісинтетазного синдрому и трудности в проведении терапии из-за отсутствия стандартов лечения и достоверных данных об эффективности препаратов.

**КЛЮЧЕВЫЕ СЛОВА:** оверлап синдром, антісинтетазный синдром, анти-Jo-1 аутоантитела, интерстициальная болезнь легких, тромбоемболія легочной артерии

## INTRODUCTION

As many as 25 % of connective tissue disease patients present with features of systemic lupus erythematosus, systemic sclerosis, polymyositis, dermatomyositis, rheumatoid arthritis and Sjögren syndrome evolving concurrently or consecutively during the course of the disease. Frequently these circumstances make the diagnosis of a specific rheumatic disease difficult. It is still contentious whether or not overlap syndromes represent the coexistence of separate diseases, the broad clinical expression of the one rheumatic disease, or distinct clinical entities with distinctive etiology and pathogenesis [1]. «Overlap syndromes» refers to a diverse group of conditions that have clinical features of, and meet classification criteria for, more than 1

well-characterized rheumatic disease. Usually present subacutely with clinical manifestations that can include different organ systems. The pattern of organ involvement reflects the characteristic features of the well-defined rheumatic diseases occurring together. Overlap syndromes are characterized by specific clinical features, autoantibody profiles, and immunogenetics. Currently it distinguished following clinical forms of overlap syndromes:

- Mixed connective tissue disease (MCTD) is a distinct clinical entity characterized by overlapping features of SLE, scleroderma, myositis, and rheumatoid arthritis in the setting of a high titer of autoantibodies to a defined nuclear antigen, known as U1-ribonucleoprotein (U1-RNP, also called RNP or nRNP). Clinical features of MCTD are highly variable, involving prominently arthritis,

Raynaud phenomenon, sclerodermatous skin changes, and myositis. Severe central nervous system and renal diseases are rare manifestations.

- Antisynthetase syndromes form a distinct group characterized by the presence of antibodies directed against various aminoacyl-tRNA synthetase enzymes (anti-Jo-1, antihistidyl-tRNA, and several others) with overlapping clinical features of myositis, arthritis, and interstitial lung disease.

- Polymyositis/scleroderma (PM/Scl) syndrome is characterized by overlapping features of scleroderma and polymyositis, and PM/Scl antibody, and by the presence of Raynaud phenomenon, tendon inflammation, and interstitial lung disease. Sclerodactyly may occur, but the truncal sclerodermatous skin changes characteristic of systemic sclerosis are absent.

Rigorous epidemiologic studies on the incidence and prevalence of overlap syndromes have not been done, and data are lacking. However, they are all rare conditions. The estimated prevalence of mixed connective tissue disease (MCTD) in a Japanese epidemiologic series was 2.7 per 100,000. Antisynthetase antibodies (including anti-Jo-1 or antihistidyl-tRNA) are found in 5 % to 20 % of patients with polymyositis or dermatomyositis [2].

## **CASE REPORT**

A 71 year old Caucasian female was seeking for medical care. She suffered from dyspnea during minor physical exertion (up to 50 m of quite walking on ground level) and no at rest, dry cough, intermittent wheezing, sensation of obstructed expiration during physical exertion, as well as at rest or at night, chest tightness, and lower extremities edema in the evening predominantly, after night it abates. Additionally she had mouth dryness, difficulty swallowing, pain and sandy sensation in the eyes, dryness of skin, numbness and tingling of the lower limbs, mostly distal parts, and the lateral aspects of the face, muscle weakness, especially during raising the hands up, intermittent joint pain in the knees, shoulders, wrist, ankles, subfebrile fever (up to 37.4°C), photosensitivity, fatigue.

Over 7 years (since 2011) patient suffered from dryness of eyes and mouth, intermittent pain in parotid salivary gland. She was surveyed and treated by rheumatologist about

Sjögren Syndrome, moderate level of activity, and received symptomatic treatment (life style modification, artificial tears liberally). During last year the patient noticed numbness and tingling of the lower limbs and face, muscle weakness, rash on eyelids, fatigue, fever, and photosensitivity. Rheumatologist diagnosed dermatomyositis, and prescribed glucocorticoids 12 mg daily, methotrexate 7.5 mg per week. Her condition was stable, symptoms did not progress. Recent month patient's health worsened, developed severe progressive dyspnea, dry cough.

Her mother suffered from musculoskeletal pain; she was not surveyed and had not precise diagnosis; she used NSAIDs locally to relieve her symptoms. Her brother suffered from skin disease with hyperkeratosis, presumably seborrhea. No family history of hypertension, diabetes mellitus. She had no allergic reactions. She had no history of smoking, alcohol or illicit drug use.

Physical examination revealed following data: Temperature 37,1°C; Pulse 70 bpm; Blood pressure 140/80 mm Hg; Respiratory rate 16 tpm; Height 160 cm; Weight 68 kg; BMI 27.

It was elderly female, which was well oriented to space and time. Her posture was active. It was occurred central type of obesity (waist circumference 112 cm). Skin was pale and dry. Drew attention face and neck erythema – V-sign; eye puffiness; periorbital violaceous erythema – heliotropes rash; hand puffiness; skin of the fingers was dry, rough, with a signs of hyperkeratosis and small fissures – Mechanic's hand, no focal thickening were detected. Conjunctiva was dry and hyperemic, but without fibrin threads and erosions or ulcers, yellowish crusts were at the eyelids. Mucous membranes of the mouth were dry, single erosions occurred. Tongue was dry and bright pink with a multiple fissures. Parotid and submandibular salivary glands were tender to palpation. Bronchial breathing in lungs to auscultation, on basal parts of both lung occur fine crackles. Peripheral pulse was full and regular. JVP + 2 cm. Apex beat was in 5<sup>th</sup> intercostal space 1 cm to the left of the left midclavicular line and had diminished force. S1 and S2 heart sounds was soft to auscultation, diffuse systolic murmur grade II at all points was detected. Abdomen was increased in size, participated in breathing actively; during palpation was soft and non-tender, hyperpneumatosis occurred, no visceromegaly.

Joints during examination were not changed; passive and active movement was painless. Peripheral muscles were atrophic, tender and dense to palpation, strength of shoulder girdle muscles was diminished, distal muscle strength was preserved. At the time of examination peripheral edema was absent. Stool was daily. Urination mildly decreased (no more than 1000 ml/24h). Unstimulated salivary flow during 15 minutes equals <1 mL.

Laboratory and instrumental methods revealed following data. Complete blood count fell down to normal ranges: RBC  $4.56 \times 10^{12/L}$ , Hb 141 g/L, WBC  $7.0 \times 10^9$ , thrombocytes  $201 \times 10^9/L$ . Urine analysis was without abnormalities: protein and glucose were absent, Leu 1–2/hpf, RBC 2–4/hpf, casts were not detected. Biochemical blood profile revealed high level of creatinekinase 261 U/L (N 26.0–140.0 U/L), AlAT 83 U/L (N < 33.0 U/L), AsAT 45 U/L (N < 32.0 U/L), LDH 296.53 U/L (N 135.0–214.0 U/L), which confirmed presence of myositis. Normal creatinine 87  $\mu\text{mol/L}$  (N 53.0–97.2  $\mu\text{mol/L}$ ) and urea 3.0 mmol/L (N 2.76–8.07 mmol/L) were detected. Also mild hypokalemia 3.0 mmol/L, hypochloremia 82.3 mmol/L and hypocalcemia 2.13 mmol/L occurred. Rheumatologic profile reflect increased ESR 35 mm/h and RF 37.0 IU/mL (N < 14 IU/mL), and normal C-RP 3.6 mg/L (N < 5.0 mg/L). Patients with dermatomyositis have higher levels of C-reactive protein and erythrocyte sedimentation rate than healthy controls, but these values were not associated with clinical or laboratory parameters of disease activity. However, erythrocyte sedimentation rate may be a valid parameter for screening pulmonary involvement [3]. Immunologic profile represented high titer of ANA 1:3200 (N < 1:100), anti-dsDNA IgG > 300 AI, anti-SS-A IgG > 8 AI, anti-SS-B IgG > 8 AI, > 8 AI. Anti-SS-A IgG and anti-SS-B IgG confirmed presence of Sjögren syndrome; anti-JO-1 IgG – antisynthetase syndrome; anti-dsDNA IgG is associated with systemic lupus erythematosus, but may be present in other rheumatic diseases [4]. PCR detected high titers of IgG to herpes virus infection 6, 5, 3. Viruses may play a part in the pathogenesis of idiopathic autoimmune rheumatic diseases [5]. Also it was revealed subclinical hypothyroidism: TSH 13.38  $\mu\text{U/mL}$  (N 0.27–4.2  $\mu\text{U/mL}$ ), T4 free 0.88 ng/dL (N 0.93–1.7 ng/dL), and boundary value TPO 31.7 IU/mL (N < 34 IU/mL). Thyroid disease,

especially hypothyroidism, is a common autoimmune condition which can be seen more frequently in patients with other autoimmune diseases [6]. Hypothyroidism may be masked by symptoms of dermatomyositis. ECG was low voltage with sinus rhythm, 70 bpm, normal heart axis, ventricular premature contraction, right atrial enlargement (II, III), and violation of repolarization in V5–V6.

Pulmonary function test showed moderate violation of lung ventilation by mixed (obstructive & restrictive) type. Echocardiography revealed hypertrophy and enlargement of both ventricles (LVPW 12.2 mm, VST 12.9 mm, RV EDD 22 mm, RVW 6 mm), signs of pulmonary hypertension, mild pericardial effusion (up to 7 mm), but preserved EF 78 %. To clarify occult malignancy, investigation with aim of tumor screen was made. Abdomen ultrasound was unremarkable. Upper GIT endoscopy represented lower esophageal sphincter failure, GERD 0 stage, duodeno-gastral reflux, and erythematous reflux gastritis. Double-contrast barium enema examination showed descending colitis. Mammography and gynecological examination were unremarkable. Three thyroid nodules in the left lobe and isthmus up to 15×13 mm were detected on thyroid ultrasound.

It should be noted, it was the first time, when pulmonary hypertension was detected in this patient. Cause of this was poorly understood. This fact led to a further search for a reason of pulmonary hypertension and severe progressive dyspnea. Anti-Jo-1 IgG is strongly associated with interstitial lung disease and pulmonary hypertension [7]. On the other hand patients with dermatomyositis has increased incidence of pulmonary thromboembolism [8]. Each of these conditions should be either confirmed or excluded. Blood test for D-dimer disclosed evidence of thrombosis: D-dimer 8.1  $\mu\text{FEU/mL}$  (N < 0.5  $\mu\text{FEU/mL}$ ). Coagulogram (prothrombin time, INR, APTT, thrombin time, fibrinogen) was unremarkable. During chest CT-scan in the lower lobe of both lungs detected areas of decreased pneumatisation with indistinct borders – ground glass pattern, up to 45\*30 mm in diameter and moderate apical pneumofibrosis. Ground glass opacity is a descriptive term referring to an area of increased attenuation in the lung on computed tomography with preserved bronchial and vascular markings. It is a non-specific sign with a wide etiology including chronic interstitial

disease, infection and acute alveolar disease [9]. CT Pulmonary angiography revealed signs of multiple segmental thromboembolism of the pulmonary artery branches (segmental arteries of 4, 5, 8, 9 segments of the left lung and 4, 6, 9, 10 segments of the right lung).

Taking into account the obtained data, final diagnosis was established. Main: Primary Sjögren's syndrome, moderate. Anti-Jo-1-antisynthetase syndrome. Interstitial lung disease. Non-massive pulmonary thromboembolism. Pulmonary hypertension. Respiratory failure type I. Chronic mild pericarditis associated with rheumatic disease. Heart failure with preserved EF (78 %) II FC NYHA. Concomitant: Autoimmune thyroiditis, hypothyroidism. Moderate GERD. Chronic refluxgastritis. Duodenogastral reflux. Descending colitis.

There are no FDA-approved therapies for the management of any of the overlap syndromes. There is a paucity of data from controlled trials to support management strategies, in which the clinical features and need for treatment are highly variable and tailored to the organ systems involved and the severity of involvement. The overall goal of therapy is symptom control and, where possible, arrest of the underlying autoimmune disease process. Among patients with antisynthetase syndrome and interstitial lung disease, prednisone is the most frequently used therapy, although additional immunosuppressive agents are increasingly being used. Symptomatic treatment included: Methylprednisolone 64 mg daily, Mycophenolate Mofetil 60 mg daily with following titration with increasing doses, Omeprazole 20 mg in the morning for gastroprotection. Pulmonary embolism management included anticoagulant therapy: Enoxaparin 60 mg bid, Warfarin 5 mg

controlled by INR 2-3. Treatment of pulmonary hypertension: Diltiazem-retard 90 mg bid, Sildenafil 5 mg tid. Taking into account that viruses can trigger autoimmune process, it was necessary to eliminate herpes infection. For the patient was prescribed Acyclovir 400 bid.

## **PROGNOSIS**

The overall outlook is defined by the severity of individual organ involvement. Some patients will have minor symptoms easily controlled with few pharmacologic interventions. Others will have progressive internal organ dysfunction, with the development of life-threatening complications that may or may not be responsive to immunosuppressive therapy [10]. In these patients the onset of pulmonary hypertension, cardiac involvement, or interstitial lung disease each portends a poorer prognosis, and they are indications for aggressive immunosuppressive therapy. Pulmonary hypertension is the commonest disease-related cause of death in patients with overlap syndrome. Patients with antisynthetase syndrome are generally considered to have a poor prognosis, with mortality 3 times greater than that of myositis/dermatomyositis without anti-synthetase syndrome [11].

Plenty of unresolved questions are being studied by scientists including: to determine the origin of chronic and persistent activation of immune system; to explain the role of immunologic, immunogenetic and neuroendocrine factors in the pathogenesis of the disease; to find a specific immune treatment of the disease.

We would like to hope that in the near future for this group of grave diseases adequate management will be developed.

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