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Clinical case of delayed systemic sclerosis and pulmonary arterial hypertension diagnostics

L. I. Vasylieva, Ye. D. Yehudina, O. S. Kalashnykova*

State Institution "Dnipropetrovsk Medical Academy of the Ministry of Health of Ukraine", Dnipro

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***E-mail:** oksana.dma@gmail.com

Pulmonary hypertension is a frequent and severe complication of systemic sclerosis (SSc). SSc-PAH patients have a worse prognosis than patients with idiopathic PAH.

We report a case of a patient with delayed SSc and PAH diagnostics. Limited SSc was established in a 61-year-woman with 20 years of Raynaud's syndrome anamnesis. But diagnosis of SSc-PAH was determined in severe and late symptomatic stage with signs of right heart congestion, NYHA III FC and mPAP 48 mmHg. This emphasizes the need for clinicians to be aware of limited SSc and have a high index of PH suspicion in such patients.

Клінічний випадок пізньої діагностики системної склеродермії та легеневої артеріальної гіпертензії

Л. І. Васильєва, Є. Д. Єгудіна, О. С. Калашникова

Ключові слова: легенева гіпертензія, системна склеродермія, катетеризація серця.

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Легенева гіпертензія є частим та загрозливим ускладненням системної склеродермії. Прогноз у пацієнтів із легеневою артеріальною гіпертензією, що асоційована зі склеродермією, гірший порівняно з пацієнтами з ідіопатичною артеріальною гіпертензією.

Наведений клінічний випадок пізньої діагностики системної склеродермії та асоційованої з нею легеневої артеріальної гіпертензії. У пацієнтки віком 61 рік з 20-річним анамнезом синдрома Рейно вперше діагностована лімітована форма системної склеродермії на стадії виражених проявів легеневої гіпертензії із середнім тиском у легеневій артерії 48 мм рт. ст., тяжкої правошлуночкової серцевої недостатності та III ФК NYHA. Це показує необхідність обізнаності та своєчасної діагностики лімітованої форми склеродермії та потребує посиленої уваги в ранньому виявленні легеневої гіпертензії в таких хворих.

Клинический случай поздней диагностики системной склеродермии и легочной артериальной гипертензии

Л. И. Васильева, Е. Д. Егудина, О. С. Калашникова

Ключевые слова: легочная гипертензия, системная склеродермия, катетеризация сердца.

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Легочная гипертензия является частым и серьезным осложнением системной склеродермии. Прогноз у пациентов с легочной артериальной гипертензией, ассоциированной со склеродермией, хуже в сравнении с пациентами с идиопатической легочной артериальной гипертензией.

Представили клинический случай поздней диагностики системной склеродермии и ассоциированной с ней легочной артериальной гипертензии. У пациентки в возрасте 61 год с 20-летним анамнезом синдрома Рейно была впервые диагностирована лимитированная форма системной склеродермии на стадии выраженных проявлений легочной гипертензии со средним давлением в легочной артерии 48 мм рт. ст., тяжелой правожелудочковой сердечной недостаточностью и III ФК NYHA. Это подчеркивает необходимость осведомленности и своевременной диагностики лимитированной формы склеродермии и требует повышенного внимания в раннем выявлении легочной гипертензии у таких пациентов.

Systemic sclerosis (SSc) is a multiorgan autoimmune connective tissue disease characterized by vasculopathy and fibrosis. The prevalence of SSc ranges from 7 million to 489 million [1].

Cardiorespiratory complications, such as pulmonary hypertension (PH) and interstitial lung disease are the main causes of mortality in SSc patients [2]. Different types of PH may occur in SSc patients: pulmonary arterial hypertension associated with SSc (SSc-PAH), pulmonary veno-occlusive disease (PVOD), pulmonary hypertension associated with interstitial lung disease (PH-ILD), pulmonary hypertension associated with left heart disease (PH-LHD). Among them SSc-PAH is the most common studied variant with prevalence of 8–15 % [3,4] and significantly lower survival rate in comparison with idiopathic PAH [5,6]. Without treatment the average life expectancy after symptoms manifestation has been 2–3 years [7]. Patients with teleangiectasia, anti-centromere antibodies, older age and longer disease duration are at the higher risk for developing PAH [8–10]. In Ukraine there is lack of epidemiological studies on PAH in SSc. According to the registry of SSc patients established in the Rheumatology Department of Mechnikov Dnipropetrovsk Regional Clinic the pulmonary artery pressure assessed by transthoracal echocardiography (TTE) was 23 mmHg in 190 patients with SSc, among them 25.3 % had pulmonary fibrosis [11].

Significant efforts have been made to improve the diagnostics and classification of PH. According to ESC/ERS guidelines 2015 PH is defined as mPAP of 25 mmHg or greater obtained by cardiac catheterisation at rest [12]. In March 2018, on the 6 World Symposium of PAH in NICE a new PH haemodynamic definition was proposed. Thus, mPAP >20 mmHG should be considered as upper normal value and pre-capillary PH could be defined as mPAP

>20 mmHg, pulmonary artery wedge pressure (PAWP) <15 mmHg and pulmonary vascular resistance (PVR) >3 WU. This definition allows to identify pulmonary vascular disease at an earlier stage. The impact of the new definition on the number of pre-capillary PH patients identified would be low with preliminary data suggesting an increase of less than 10 % [13]. In the study of Coghlan et al., 71 patients with SSc were clinically assessed at baseline and after 3 years, including right heart catheterisation (RHC). Among them 3 % developed PH and 7 % developed SSc-PAH. PVR, tricuspid regurgitation velocity, diffusion capacity and the size of the inferior vena cava at baseline were independent predictors for the development of PH during follow-up [14].

Another study of J. V. Cristopher et al. demonstrates, that 16 SSc patients with borderline mPAP from 21 to 24 mmHg have developed manifest PAH at the time of follow-up RHC (median follow up 45 months). At baseline catheterization these 16 patients with borderline PH had mPVR of 2.9 WU and it increased to 4.9 WU at follow up. Patients with borderline mPAP were more likely to develop PH than patients with mPAP ≤20 mm Hg [15].

SSc-PAH belongs to Group 1 disease of the PH classification, at the same time the number of SSc patients with mPAP > 20 mmHg and PAWP > 15 mmHg at rest is in the range of 20–45 % [16,17]. After significant parenchymal lung disease exclusion, they will be classified as PH due to SSc-PH-LHD, or Group 2 of the PH classification [12]. The underlying causes of LHD can include the presence or absence of valvular heart disease, heart failure with reduced ejection fraction or heart failure with preserved ejection fraction. Elevation in pulmonary vascular pressures can be related to several mechanisms: passive transmission of pressures from the left atrium, changes in vascular compliance due to elevated left atrial pressure [18] and changes in the pulmonary vascular tone or vascular remodeling.

Another challenge to the PH specialist may be diagnostics and treatment of PVOD in suspected SSc-PH patients. This condition remains poorly understood and accounts for 5–10 % of cases initially misdiagnosed as IPAH. Haemodynamic presentation of PVOD is similar to IPAH, particularly with respect to wedge pressure, which is invariably normal in both disease conditions [19,20], that was reflected in the ESC/ERS guideline PH 2009 [12]. In updated clinical classification (Nice 2018) PVOD was determined as PAH with overt sings of venous / capillaries (PVOD/PCH) involvement [13]. Recent genetic studies have shown that PVOD occurs sporadically or is inherited in families due to recessive mutations of the eukaryotic translation initiation factor 2 alpha kinase 4 (EIF2AK4) gene which encodes the GCN2 protein [21]. Clinicians should be aware in cases, when patient experiences worsening after initiation of the specific PAH treatment or becomes refractory to this therapy.

Major finding that has important implications for both the initial clinical classification of SSc-PH patients and their long-term management is change in hemodynamic classification over time. In the PHAROS cohort [22], 30 % of patients changed their PAWP on follow-up RHC to the degree where they cross over the PAWP classification threshold of 15mmHg, including almost one-quarter of patients who had an initial PAWP ≤15 mmHg. This occurred independently of whether the patient was placed on a PH medication. In the REVEAL registry, 16 % of PAH patients with mixed etiology changed their PAWP enough on follow-up to have what is termed a “PAWP class change”, at the same time 65 % of patients with a PAWP >15 mmHg had a PAWP <15 mmHg on repeat RHC [23]. There are several explanations why PAWP may truly change in SSc-PH patients. First, patients who develop an elevated PAWP over time may simply have developed heart failure with preserved ejection fraction in addition to their underlying PH, since heart failure is a disease associated with aging and diastolic dysfunction which is common in SSc [24]. But in the PHAROS study no increased baseline diastolic dysfunction was found in patients with an initial PAWP <15 mmHg who had an elevated PAWP on their follow-up RHC, there were no differences in TTE measurements of diastolic dysfunction or left atrial size when performed at the time of the second RHC, making progressive development of heart failure with preserved ejection fraction less likely [23]. Second, either improvements or decrements over time in right ventricular (RV) function can alter left heart filling pressures by RV-LV interdependence [25]. And the last one, therapies such as diuretics and PH medications may have altered PAWP.

SSc being a well-known risk factor for developing PAH, but there are still delays in diagnosing PAH and consequently more than 80 % of patients present with the World Health Organization (WHO) functional class III or IV at this point [26]. Coghlan et al. reported the first evidence-based algorithm (DETECT) for the screening of PAH in SSc [9]. The DETECT algorithm is a tool to identify patients with PAH in the asymptomatic stages, through the study of clinical variables, pulmonary function tests, immunological, biological, electrocardiographic and finally, echocardiographic parameters. The application of the DETECT algorithm was conducted in two steps through the website PAH risk calculator (http://detect-pah.com) [27], the first step for referring the patient for echocardiography and the second for carrying out RHC [26]. The ESC/ESR 2015 PH guidelines introduce the DETECT algorithm as a valid method to be performed for annual screening of PAH in patients with SSc [12].

It is a very common situation for SSc patients, when several mechanisms can work together and lead to PH. Careful phenotyping of PH in SSc is very important because it has an impact on treatment choice, therefore different treatments and strategies are indicated for the different subgroups of patients.

Despite the attention that PH has drawn in recent years, significant gaps remain in the management of challenging cases of PH in Ukraine.

In September 2016 a 63-year-old female presented to the centre with mixed dyspnea on a moderate exertion progressively increased over the last year; fatigue; episodes of burning or tightness in the chest and pain lasting more than a few minutes, getting worse with activity; chronic ankle edema; two pillow orthopnea for 2 months; pain in fingers and toes, their paleness, sensations of cold and numbness; back pain; dizziness while walking.

In 2015, the patient was hospitalized due to angioparalitic stage of Raynaud’s syndrome to the Rheumatology Department of the City Hospital. She had peripheric artery disease with involvement of forearm and tibial arteries

without hemodynamic abnormality. She noted a history of Raynaud's syndrome and sclerodactyly for more than 20 years, but she was not examined for scleroderma. Her medical history also included anamnesis of arterial hypertension for 35 years and ischemic stroke (March 2015). The patient was in menopause for 10 years, had one pregnancy with 1 normal birth in anamnesis.

Physical examination of the patient identified sclerodactyly, cyanosis, jugular vein pulsation. Thyroid gland was normal without masses. There was no adenopathy. Chest was hyposthenic and symmetric, nontender without masses or discharges. BMI was 26.7. RR was 22 per minute. Lung fields were clear to auscultation. BP was 145/95 mmHg sitting, HR was 92 per minute. Cardiac auscultation revealed systolic murmur on the left parasternal border and enhanced P2. Abdomen was symmetrical, soft, flat, bowel sounds were present, no bruits, nontender to palpation. Flunk dullness was noted on percussion. Liver edge was +2 cm, spleen, kidney did not palpate. Extremities examination revealed sclerodactyly, signs of chronic venous stasis changes in both legs, 1+ edema until the knees.

Bendopnea test [28,29]: BP was 130/85 mmHg and BR was 4 within 15 seconds in sitting position. While bending 30 seconds dyspnea occurred on the 10 second. After the patient returned in sitting position BP was 138/92 mmHg, BR was 7 within 15 seconds.

The 6-MWT distance was 192 meters with desaturation from 95 % to 91 % and pulse increased from 96 to 118 beats per minute. Borg dyspnea score was assessed as 4.

Chest radiography revealed increased cardiothoracic ratio, clear lung fields with prominent central pulmonary arteries.

On ECG, there was left axis deviation, rhythm was sinus with HR 87 per minute and amplitude signs of right atrium enlargement.

The result of spirometry (FEV1 84 %, FEV1/ FVC 126) did not reveal any abnormalities.

Clinical blood analysis: HGB 158 g/L, RBC 4.8 10^{12}/L, WBC 7.1 10^{9}/L; Platelets 202 g/L.

Biochemical analysis: total bilirubin 8 umol/L, LDL 3.1 mmol/L, alkaline phosphatase 114 U/L, ALT 18 U/L/, AST 30 U/L, creatinine 107 umol/L, urea 350 µmol/L, total protein 65 g/L, albumin 39 g/L, sodium 140 mmol/L, potassium 5.0 mmol/L. Differential diagnoses of HIV, hepatitis B and C virus, thrombophilia, thyroid disorders were excluded by laboratory tests. NT-proBNP was 845 pg/ml (RR <130 pg/ml). Index-anticentromer antibody IgG > 8.

Based on ACR (including the LeRoy and Medsger modifications) and the EULAR Criteria for Systemic Sclerosis [30], limited SSc was diagnosed as the presence of Raynaud's syndrome plus SSc-specific autoantibodies.

Screening for PH using step 1 of the DETECT algorhithm showed 329 risk score.

Further testing included TTE which showed a markedly dilated RV (end-diastolic diameter 51 mm) and right atrium (right atrium area 31 cm^2), reduced tricuspid annular plane systolic excursion (TAPSE) (10 mm), severe tricuspid regurgitation (>2.6 mm/sec), RV/LV was 1.0, at the same time estimated systolic pulmonary artery pressure (sPAP) was 107 mmHg, abnormal function of the interventricular septum (IVS), a nonhaemodynamic relevant pericardial effusion (100 ml), and a dilated vena cava inferior (9.7 mm) were revealed. Left ventricle (LV) ejection fraction was 74 %, iLV mass – 64 g/cm^2. There were no signs of congenital heart disease.

After calculating the total risk score by step 2 of the DETECT algorithm, RHC was performed.

Hemodynamic evaluation by RHC verified pre-capillary PH: mPAP 48 mmHg, PAWP 9 mmHg and PVR of 800 dyn*sec/cm^5, cardiac index 2.0 l/min/m^2. Mixed venous partial pressure of oxygen was 31 mmHg, arterial partial pressure of oxygen was 51 mmHg. Ventavis inhalation performed during RHC did not meet the criteria for an acute vasoreactive response.

Coronaroangiography findings included 65 % stenosis of left anterior descending artery and 30 % stenosis of left circumflex artery.

Abdomen ultrasound showed echo-signs of fatty liver disease. Portal vein was 1.0 cm. The wall of gallbladder was thickened up to 0.4 cm and hyperechoic, echogenicity of pancreas was increased without masses. Marked aortic sclerosis was seen.

As a result, the patient's diagnosis was confirmed as mild PAH WHO FC II, associated with limited SSc, intermediate risk. III stage of right heart failure with RV systolic dysfunction and LV preserved systolic function.

PAH treatment was initiated with Revatio 60 mg daily. Concomitant therapy consisted of Valsartan / Hydrochlorothiazide 160/12.5 mg daily, Acetylsalicylic acid 75 mg daily, Atorvastatin 20 mg daily, Thorasemide 10 mg daily, Furosemide 40 mg daily, Spironolactone 50 mg daily. The patient had rheumatologist consultation, but no medications for SSc were administered.

The patient had remained clinically stable for 4 months. In March 2017, she was admitted to the hospital with tachycardia, worsening of right heart failure, signs of fluid retention and increased dyspnea, deterioration to NYHA III. There was atrial fibrillation on ECG with HR of 110 beats per minute and BP of 134/85 mmHg. Anticoagulation with Rivaroxaban 20 mg daily was initiated immediately. Due to aggravation of heart failure symptoms, early cardioversion was considered.

On transesophageal examination, right ventricle outflow tract thrombus and left atrial appendage thrombus were found. These results pointed on management the patient with rate control therapy. After escalation of diuretic therapy and achievement of rate control between 90–100 beats per minute, some improvement of right heart failure congestion symptoms was observed, but the patient still remained in NYHA III. In 6-MWT the covered distance was 170 m. TTE hemodynamic parameters did not differ from baseline: RV/LV 1.0; sPAP 105 mmHg, iS RA 19.4 cm/m^2, LVEF 65 %, paradoxical motion became more pronounced.

After clinical examination, we observed progression to NYHA FC III in our patient, but there were no TTE changes and no 6-MWD test decrease to 15 %. Right heart catheterization was not done due to presence of RVOT thrombus. Decision about sequential drug combination therapy was done and Ventavis was administered additionally.

The patient had remained in the same clinical status without improvement following initiation of combination therapy. In October 2017, she suddenly died.

Our clinical case demonstrates outcomes of delayed SSc and PH diagnostics. Thus, limited SSc was established

in the 61-year-woman after 20 years of Raynaud's syndrome anamnesis. During hospitalization with paralytic form of Raynaud's syndrome in 2015, our patient had already complained of dyspnea, but none of these symptoms were taken in a point for SSc suspicion and subsequent screening for PH with the DETECT algorithm. Diagnosis of PAH was determined in severe and late symptomatic stage with signs of right heart congestion, NYHA III FC and mPAP 48 mmHg. This emphasizes the need for clinicians to be aware of limited SSc and have a high index of PH suspicion in such patients. Ongoing follow-up and critical re-evaluation of the diagnosis with individual assessment of clinical status, co-morbidities and treatment efficacy are essential due to the high risk of cardiovascular complications.

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Information about authors:
Vasylieva L. I., MD, PhD, Associate Professor of the Department of Internal Medicine 3, SI "Dnepropetrovsk Medical Academy of Health Ministry of Ukraine", Dnipro.
Yehudina Ye. D., MD, PhD, Associate Professor of the Department of Internal Medicine 3, SI "Dnepropetrovsk Medical Academy of Health Ministry of Ukraine", Dnipro.
Kalashnykova O. S., MD, PhD, Professor Assistant of the Department of Internal Medicine 3, SI "Dnepropetrovsk Medical Academy of Health Ministry of Ukraine", Dnipro.

Відомості про авторів:
Васильєва Л. І., канд. мед. наук, доцент каф. внутрішньої медицини 3, ДЗ «Дніпропетровська медична академія МОЗ України», м. Дніпро.
Єгудіна Є. Д., канд. мед. наук, доцент каф. внутрішньої медицини 3, ДЗ «Дніпропетровська медична академія МОЗ України», м. Дніпро.
Калашникова О. С., канд. мед. наук, асистент каф. внутрішньої медицини 3, ДЗ «Дніпропетровська медична академія МОЗ України», м. Дніпро.

Сведения об авторах:
Васильева Л. И., канд. мед. наук, доцент каф. внутренней медицины 3, ГУ «Днепропетровская медицинская академия МЗ Украины», г. Днипро.
Егудина Е. Д., канд. мед. наук, доцент каф. внутренней медицины 3, ГУ «Днепропетровская медицинская академия МЗ Украины», г. Днипро.
Калашникова О. С., канд. мед. наук, ассистент каф. внутренней медицины 3, ГУ «Днепропетровская медицинская академия МЗ Украины», г. Днипро.

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