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HEART INJURY IN JUVENILE SYSTEMIC SCLERODERMA (clinical case)

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Ключевые слова: *ювенильная системная склеродермия, дилатационная кардиомиопатия, дети*

Abstract. Heart injury in juvenile systemic scleroderma (clinical case). Omelchenko L.I., Mukvich O.N., Belska O.A., Dudka I.V., Klymyshyn Y.I., Rudenko N.M., Kalashnikova R.V., Ismakaieva D.L., Vdovina N.M., Liudvik T.A. *Juvenile systemic sclerosis (JSS) has many clinical manifestations that differ from adults. Early diagnosis is problematic. The course of the disease and the severity of the prognosis depend on the involvement of internal organs in the process, first of all, the heart, lungs, kidneys. Cardiac pathology is a frequent and prognostically unfavorable target of the scleroderma process in adults, but it is rarely diagnosed in children. The aim of the work was to study the features of the clinical manifestations of systemic sclerosis in a child with severe heart disease. A polymorphism of the clinical symptoms of severe heart damage with the development of dilated cardiomyopathy in a one-year-old child with systemic sclerosis is presented. The features of the case are the early debut of systemic sclerosis in a child with a burdened hereditary history of autoimmune pathology (psoriasis in the father and grandmother), rapid progression of the autoimmune process, severe heart damage by the type of non-compact (dilated) cardiomyopathy, positive clinical dynamics when using pathogenetic therapy. Early detection of cardiovascular lesions using modern diagnostic methods, timely implementation of adequate therapy in a multidisciplinary team and regular cardiovascular screening can improve the prognosis, quality of life and reduce mortality.*

Реферат. Поражение сердца при ювенильной системной склеродермии (клинический случай). Омельченко Л.И., Муквич Е.Н., Бельская Е.А., Дудка И.В., Климишин Ю.И., Руденко Н.М., Калашникова Р.В., Исмакаева Д.Л., Вдовина Н.М., Людвик Т.А. *Ювенильный системный склероз (ЮСД) имеет множество клинических проявлений, которые отличаются от таковых у взрослых. Диагностика на ранних стадиях – проблематична. Течение заболевания и тяжесть прогноза зависят от вовлечения в процесс внутренних органов, прежде всего сердца, легких, почек. Поражение сердца является частой и прогностически неблагоприятной мишенью склеродермического процесса у взрослых, но у детей диагностируется редко. Целью работы явилось изучение особенностей клинических проявлений системного склероза у ребенка с тяжелым поражением сердца. Представлен полиморфизм клинической симптоматики тяжелого поражения сердца с развитием дилатационной кардиомиопатии у годовалого ребенка с системным склерозом. Особен-*

ностями случая являются ранний дебют системного склероза у ребенка с отягощенным наследственным анамнезом по аутоиммунной патологии (псориаз у отца и бабушки), быстрое прогрессирование аутоиммунного процесса, тяжелое поражение сердца по типу некомпактной (дилатационной) кардиомиопатии, положительная клиническая динамика при применении патогенетической терапии. Раннее выявление сердечно-сосудистого поражения при применении современных методов диагностики, своевременное проведение адекватной терапии в мультидисциплинарной команде и регулярный сердечно-сосудистый скрининг позволяет улучшить прогноз, качество жизни и снизить летальность.

Systemic scleroderma (from the Greek sclerosis - hardening, compaction and derma – skin) is a progressive polysyndromic disease with characteristic changes in the skin, musculoskeletal system, internal organs (lungs, heart, digestive tract, kidneys), common vasospastic disorders by type of Raynaud's syndrome, which is based on connective tissue damage with a predominance of fibrosis [1, 5, 14]. The incidence of systemic scleroderma in adults is 0.45-1.4 per 100 thousand population, and in children – 0.5-1.9 per 100 thousand children per year [5, 4]. The etiology and pathogenesis of systemic scleroderma at the present stage are insufficiently studied [11, 12]. It is assumed that the development of the disease is due to genetic predisposition in combination with the influence of adverse exogenous and endogenous factors, especially immune, environmental (infections, chemicals, trauma, vibration, cooling, etc.), neuroendocrine, psychosocial [8 , 11, 12]. The main links in the pathogenesis are the processes of enhanced collagen- and fiber formation, microcirculation disorders and immunoregulation [3, 10].

Systemic sclerosis in children under 16 years of age – juvenile systemic sclerosis (JSS) – is characterized by features of clinical symptoms: focal skin lesions with the formation of hemiforms, unapparent Raynaud's syndrome, articular syndrome with the development of contractures [1, 2]. The course of the disease and the severity of the prognosis depend on the involvement of internal organs (heart, lungs, kidneys), but visceral pathology, which can often be subclinical for a long time, is difficult to diagnose [6, 10, 13].

The heart is a frequent and prognostic target of the scleroderma process. However, the prevalence of cardiac lesions recorded in systemic scleroderma varies greatly in different studies and ranges from 7.0 to 39.0% and is often underestimated due to diversity and asymptomatic nature [6, 13]. Myocardial fibrosis on autopsy is detected in more than 80.0% of cases, although in vivo diagnosis of the heart disease by type of scleroderma cardiosclerosis is found in only 30-40.0% of patients [3]. Clinically significant heart disease is associated with prognosis severity and mortality of up to 70.0% of patients within 5 years. About 25.0% of deaths associated with systemic sclerosis are due to cardiac causes with the development of heart failure [2]. Involvement of the heart in the pathological process in systemic sclerosis can be caused by both primary lesions (myocarditis, endocarditis, pericarditis) and secondary – in the formation of pulmonary arterial hypertension and systemic hypertension in patients with kidney disease [6].

Peculiarities of primary heart disease are ventricular myocardial fibrosis, which causes systolic and diastolic left ventricular dysfunction with decreased ejection fraction, arrhythmias and conduction disorders, which are characteristic pathomorphological signs of sclerodermic heart lesion. The mechanisms underlying arrhythmia in systemic scleroderma are multifactorial and include the direct impact of microvascular trauma, further development of fibrosis and autonomic dysfunction [7]. The most common arrhythmias are supraventricular tachycardia, tachyarrhythmia, extrasystole (polytopic and group), prolongation of the P-Q interval, complications of intraventricular conduction, blockade of the anterior branch of the left branch of His bundle. Intraventricular conduction defects are clinically significant because they are associated with the development of atrioventricular block and other life-threatening arrhythmias [9, 13].

Clinically, the involvement of the heart in systemic sclerosis in most cases is asymptomatic or paucisymptomatic. Patients experience discomfort, prolonged dull pain in the heart, palpitations, arrhythmias, shortness of breath. Timely diagnosis of lesions of the cardiovascular system can be carried out only with careful monitoring of patients using modern instrumental research methods – electrocardiography, echocardiography, scintigraphy, magnetic resonance imaging and others. [12]. Some patients with high autoimmune activity are diagnosed with a subclinical course of myocarditis, which occurs only in the presence of symptoms of polymyositis [13]. Changes in the endocardium in the form of fibroplastic endocarditis with the subsequent formation of valvular sclerosis in children is not common. It is possible the development of valvular heart apparatus with the formation of sclerodermic defect most often of mitral valve, which runs well and does not lead to decompensation.

Pericardial lesions by the adhesive type (rarely exudative) of pericarditis usually have asymptomatic or paucisymptomatic course and in adults are detected mainly during echocardiography but in children it is not often diagnosed [1, 6]. Pathological changes in the cardiovascular system are the main cause of sudden death syndrome in children. Heart failure is not characteristic of JSS, but in case of development it is resistant to therapy and determines an unfavorable prognosis [13].

Heart lesions that develop as a result of pulmonary arterial hypertension (isolated or with interstitial lung damage) or renal pathology are uncommon in children: among adult patients with scleroderma the prevalence of pulmonary arterial hypertension is 10-15%, among children – up to 7 %. Up to 30.0% of patients with an unfavorable prognosis in pulmonary arterial hypertension have connective tissue diseases, mainly scleroderma [6, 7, 15].

Thus, the polymorphism of cardiac lesions in juvenile systemic sclerosis with minimal skin signs or even their absence significantly complicates early diagnosis, adequate therapy, prognosis and quality of life of patients [3].

Case history: an early debut of juvenile systemic scleroderma with lesion of the heart as a target organ in a girl B., aged 1 year 9 months.

The study was conducted in accordance with the principles of bioethics set out in the Helsinki Declaration on Ethical Principles for Human Health Research and the Universal Declaration on Bioethics and Human Rights (UNESCO).

Case history: A child born to gravida 2 para 2, cesarean section at the 38th week of gestation with a weight of 3 kg 400 g, height 52 cm. Breastfeeding up to 1 year, psychophysical development corresponded to age. Vaccinated according to a calendar. Pediatric infections, allergic reactions – the mother denies.

Family history is burdened: maternal and paternal grandparents suffer from psoriasis. After 6 months of age, the child often suffered from acute respiratory diseases with febrile convulsions, obstructive bronchitis, for which she was often hospitalized and received antibiotic therapy, inhalation with berodual, glucocorticoids. From the age of 1 year and 3 months, the mother began to notice small areas of thinning of the skin on the child's right leg and around the right ankle joint, about what the mother sought medical advice at the outpatient clinic at the place of residence. At the age of 1 year and 4 months, against the background of an acute respiratory disease, the child's condition suddenly deteriorated: she became anergic, pale, with shortness of breath, cyanosis of the lips and extremities, increased sweating. When conducting echocardiography at the place of residence, non-compact (dilated) cardiomyopathy, myocarditis was suspected. The child was sent to the State Institution "Scientific and Practical Medical Center of Pediatric Cardiology and Cardiac Surgery of the Ministry of Health of Ukraine", where due to the severity of the condition caused by signs of heart failure, she was hospitalized in the intensive care unit.

On hospitalization according to electrocardiography: sinus rhythm, sinus tachycardia (heart rate 130 beats per minute), deviation of the electrical axis of the heart to the left, overload of the left heart. According to echocardiography, a pronounced dilatation of the left heart was diagnosed: end-diastolic size of the left ventricle 43 mm, end-diastolic volume of the left ventricle 83 ml, end-diastolic index of the left ventricle 166 ml/m^2, significantly reduced left ventricular contractility (ejection fraction 25%). Increased trabecularity of the left ventricular cavity (myocardial incompatibility) was noted. On the mitral valve – a small outflow, other valves – within normal. Open oval window 3 mm (Fig. 1).

According to the radiography of the thoracic cavity: X-ray signs of cardiomegaly with a sharply expanded shadow of the heart, cardiothoracic index 0.7 (Fig. 2).

To clarify the diagnosis and the nature of the lesion, magnetic resonance imaging of the heart was performed, the results of which showed the expansion of the left ventricular cavity with significantly reduced contractility. Non-compactness of the entire left ventricular myocardium was determined, except for the interventricular septum, the maximum thickness of the "non-compact" zone up to 0.9 cm, with the thickness of the "compact" – 0.3 cm (measurements during diastole) (ratio of non-compact to compact zone 3.0). Functional indicators of the left ventricle: ejection fraction – 21% (norm 56-78%), end-diastolic volume – 50 ml, end-diastolic index – 103 ml/m^2 (norm 41-81 ml/m^2), cardiac index – 2.2 (norm – 1.75-3.8) l/min/m^2. No disorder of perfusion was detected in the introduction of a contrast medium. On the late post-contrast images, pathological accumulation of contrast medium by the myocardium was not observed, a small amount of fluid in the pericardium was detected. Conclusion: the detected changes may correspond to non-compact cardiomyopathy with the transition to dilatation one, no signs of acute myocarditis.

Against the background of therapy (medrol, furosemide, asparkam, verospirone, captopril, aspirin, L-carnitine) the child's condition stabilized, she became more active, appetite appeared, signs of heart failure decreased, positive echocardiographic dynamics: the left ventricular ejection fraction increased from 25% to 35%, the left ventricular cavity (end-diastolic size/end-diastolic index) decreased from 43 mm/166 ml/m^2 to 34 mm/94 ml/m^2.

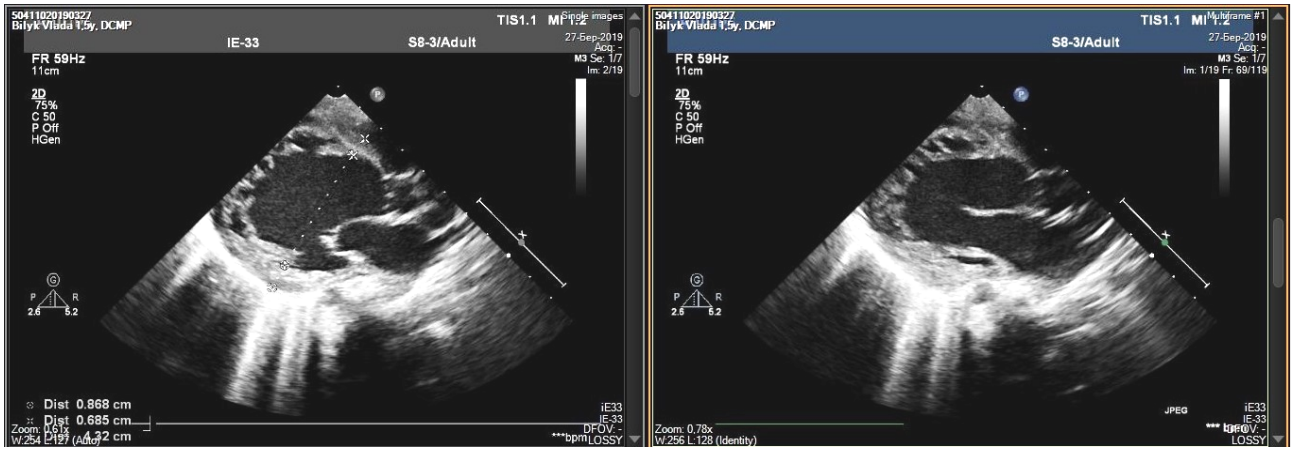

**Fig. 1. Echocardiography along the long axis of the left ventricle.
Significant dilatation of the left ventricular cavity, end-diastolic size 43 mm.
Non-compactness of the walls of the left ventricular myocardium**

The presence of skin changes in a child with heart disease required consultation with a pediatric rheumatologist and geneticist to make a differential diagnosis between scleroderma and Bart's syndrome. For the final verification of the diagnosis and treatment, the child was sent for hospitalization in the State Institution "IPOG named after acad. O.M. Lukyanova of National Academy of Medical Sciences of Ukraine ".

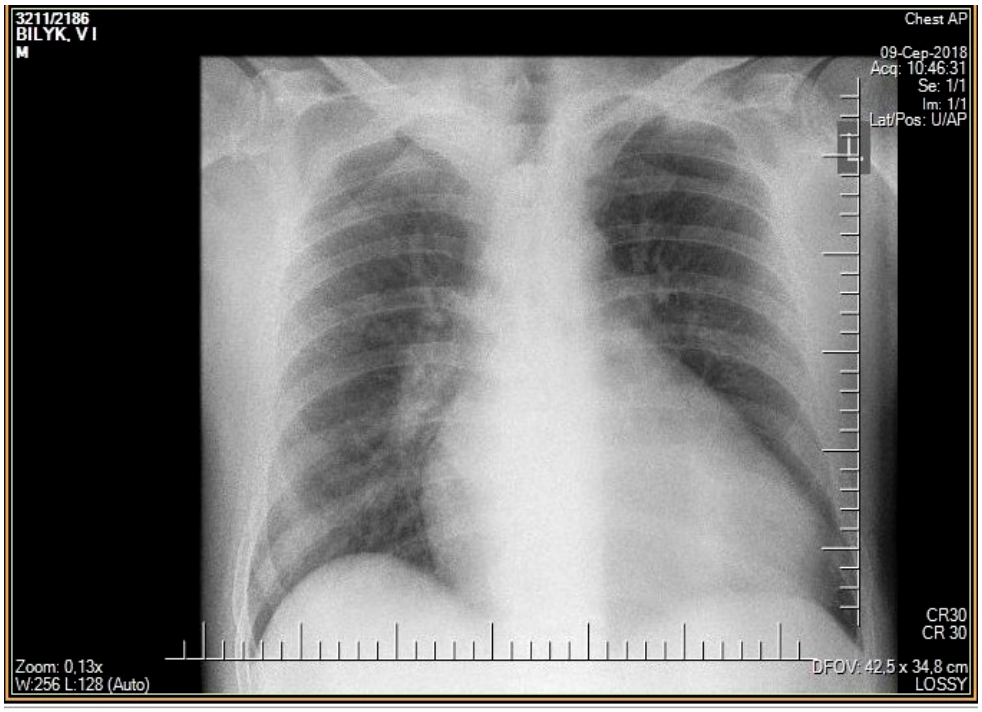

Fig. 2. X-ray examination of the thoracic cavity organs

Patient's state on hospitalization of moderate severity. Heart rate – 100-96 beats per minute, respiratory rate – 26 per minute, blood pressure (BP) 90/50 mm Hg., weight – 12 kg, height – 86 cm. The body build is normosthenic, satisfactory nutrition. Pale pink skin, focal skin changes on the legs (up to 5 cm in diameter), around the ankle and right knee joints in the form of induration, atrophy, inability to fold the skin and lack of subcutaneous fat, increased vascular pattern Fig. 3).

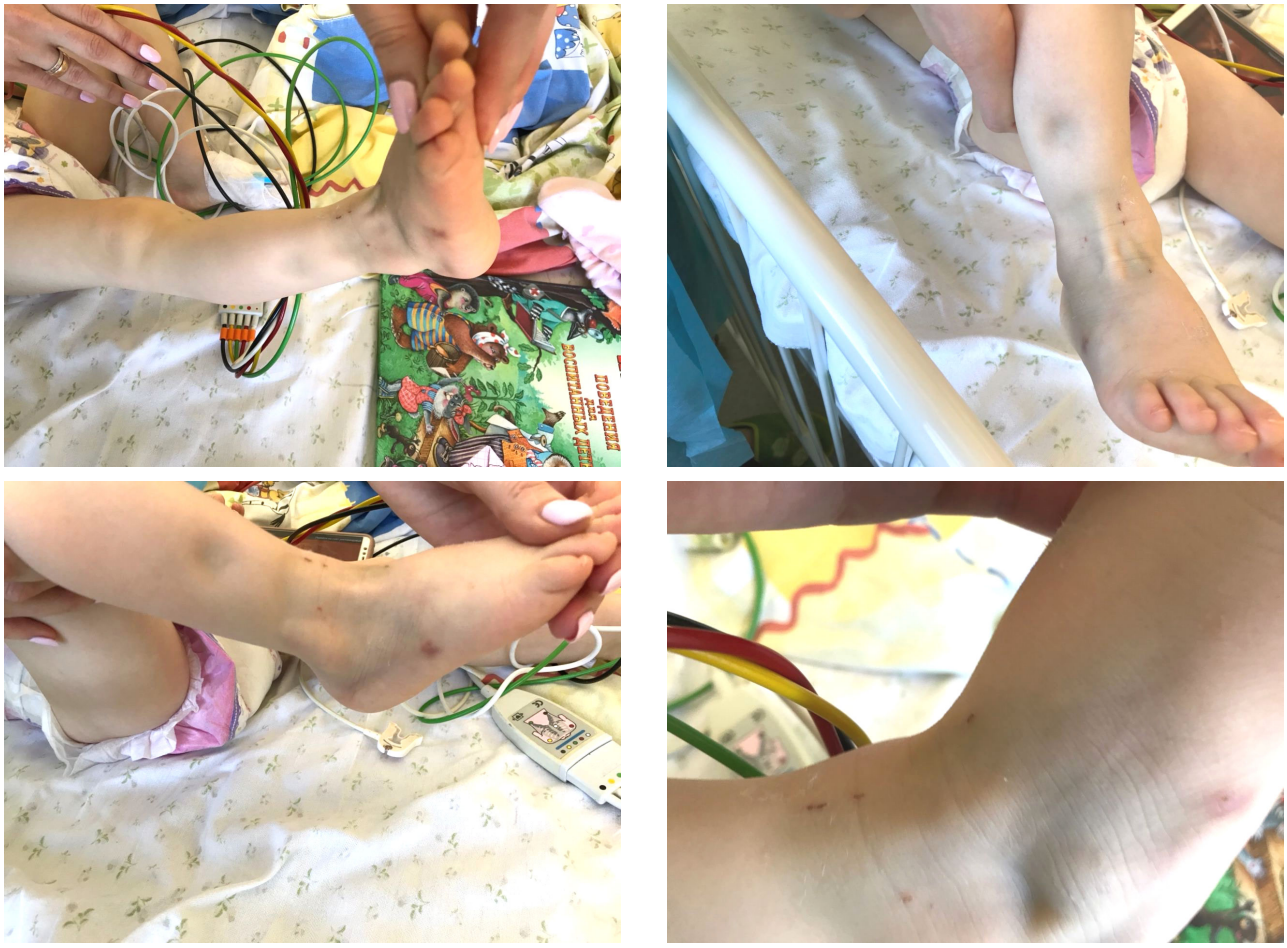

Fig. 3. Foci of induration, atrophy of the skin and subcutaneous fat (up to 5 cm in diameter) in the areas of the legs, around the ankles and right knee joints

Peripheral lymph nodes are not enlarged. Joints of the correct contour, painless, passive and active movements in full. Muscle tone is preserved, symmetrical. Harsh breathing in the lungs, no wheezing. Heart tones are sonorous, rhythmic, accent of the second tone over the pulmonary artery, systolic murmur in the second intercostal space on the left. The abdomen is soft, painless, accessible to deep palpation. The liver is 1.5 cm below the edge of the costal arch, the edge is elastic, painless, the spleen is not palpable. Diuresis and defecation is normal.

Examination. Full blood count – $5.18x10^{12}$/l, hemoglobin – 148g/l, leukocytes – 15.0×10^{9}/l, platelets – 259×10^{9}/l, eosinophils – 1%, neutrophils – 28.0%, lymphocytes – 59.0%, monocytes – 9.0%, basophils – 2.0%, erythrocyte sedimentation rate – 2 mm/h. Biochemical blood test: protein – 64 g/l, C-reactive protein – negative, total bilirubin – 13 μmol/l, cholesterol – 3.39 μmol/l, thymol test – 5.3 Units, transaminases (ALT and AST) – normal, urea – 5.91 kmol/l, creatinine – 0.049 μmol/l, glucose – 4.2 μmol/l. Coagulogram: prothrombin index – 102.6%, recalcification time – 0.98 s, total fibrinogen – 2.44 g/l, fibrinogen "B" – negative, fibrin – 11 mg. Total IgE – 159.5 IU/l (N=0-60 IU/l). Rheumatoid factor – undetermined, antistreptolysin – up to 200 U/l, precursor of brain natriuretic peptide (NT-proBNP) – 10500 pg/ml (norm<125 pg/ml). Urine tests (general, according

to Nechiporenko, according to Zymnytsky) – without pathological changes.

Sclerodermic blot: RP11, RP155, Scl-70, CENP B, Fibrillarin (U3-RNP), NOR90, Th/To, PM-Scl100, PM-Scl 75, PDGFR, Ro-5 – not detected, Ro-52 – positive, antinuclear antibodies 1:100, antibodies to double-stranded deoxynucleic acid – 0.88 (N<1.1 g/l). IgG – 12.9 g/l (N=4.53-9.16 g/l), IgA – 0.73 g/l (N=0.2-1.6 g/l), IgM – 2.29 g/l (N=0.19-1.46 g/l).

Positive dynamics was noted during heart examination. Electrocardiography: sinus arrhythmia, normal position of the electrical axis of the heart, pronounced metabolic changes in the myocardium. Echocardiography: heart cavities within the age norm, end-diastolic size of the left ventricle – 28 mm, end-diastolic volume of the left ventricle – 30 ml, end-diastolic index of the left ventricle – 55 ml/m^2, ejection fraction – 55%. Heart valves – within norm. Minimally open oval window (Fig. 4).

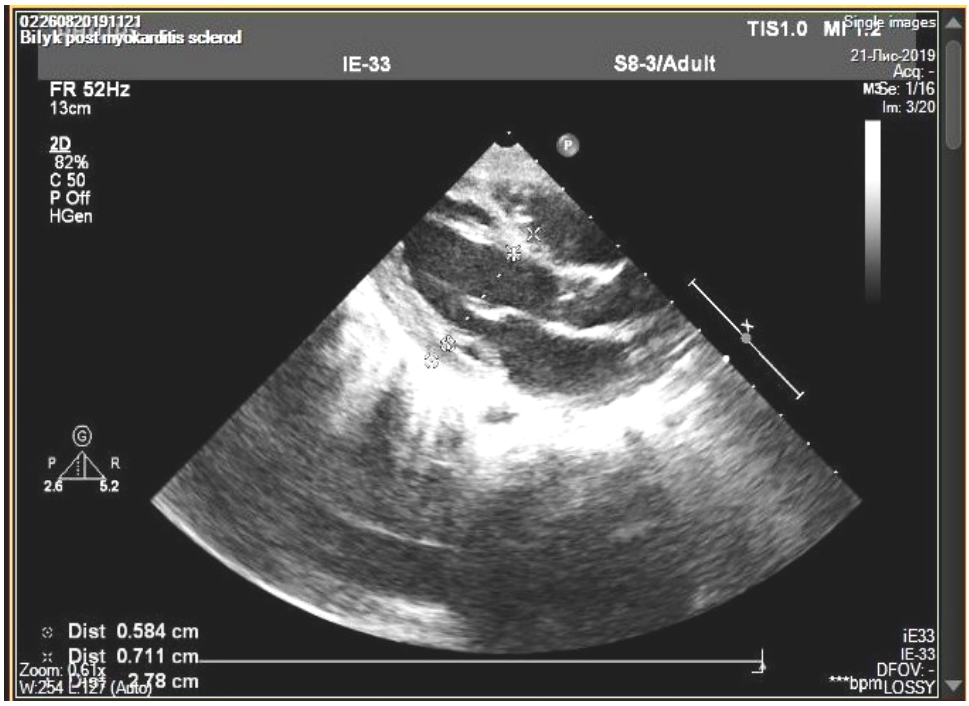

Fig. 4. Echocardiography along the long axis of the left ventricle. Positive echocardiographic picture against the background of treatment: heart cavity within the age norm, end-diastolic size of the left ventricle 28 mm, end-diastolic volume of the left ventricle 30 ml, left ventricular end-diastolic index 55 ml/m^2, emission fraction 55%

According to the radiography of the thoracic cavity, there was also a positive dynamics compared to the previous examination at the Center for Pediatric Cardiology and Cardiac Surgery, cardio-thoracic index – 0.4 (Fig. 5).

According to the ultrasound diagnostics of the abdominal cavity, ultrasound signs of moderate hepatosplenomegaly were detected, no reactive changes on the part of the mesenteric lymph nodes were detected. Ultrasound diagnosis of the thyroid gland and joints revealed no pathology. On carrying out capillaroscopy – signs of Raynaud's syndrome I-II stage are revealed.

The result of skin and muscle biopsy: in bioptates of the skin and subcutaneous tissue – foci of disorganization and sclerosis of the dermis, in deeper areas on the border and in the thickness of adipose tissue – foci of granulomatous inflammation. Muscle biopsies identify areas of fibrosis, fatty degeneration, variability in fiber thickness, splitting of individual fibers, manifestations of vasculitis with foci of lymphocytic infiltration. Conclusion: histological picture corresponds to scleroderma.

The child is consulted by a geneticist. The result of DNA analysis did not reveal pathogenic and likely pathogenic variants of the nucleotide sequence in the TAZ gene. The activity of the lysosomal enzyme α-glucosidase is within the reference values. Pompe disease is ruled out.

Given the presence of focal changes in the skin of the legs (up to 5 cm in diameter), around the ankle and right knee joints in the form of induration, atrophy, enhancement of vascular pattern, laboratory (presence of positive markers of sclerodermic blot), pathohistological data, lesion of the heart by type of secondary cardiomyopathy with left ventricular contractile dysfunction and cavity dilatation (ventricular myocardial fibrosis, characteristic pathomorphological signs of scleroderma), the child was diagnosed with juvenile systemic scleroderma, (induration, atrophy, fibrosis), blood vessels (Raynaud's syndrome), heart (dilated cardiomyopathy, heart failure II.).

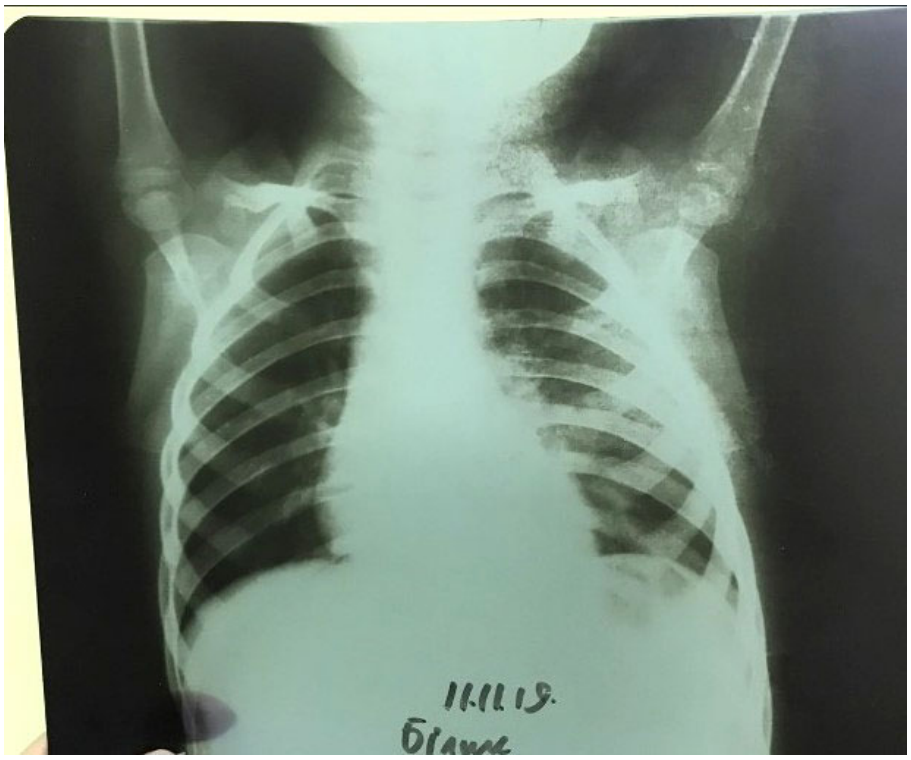

Fig. 5. X-ray examination of the thoracic cavity organs in dynamics: cardiac shadow within norm

Administered treatment: prednisolone (10 mg per day with gradual reduction of the dose by ¼ of tablet 1 time per week to 2.5 mg), methotrexate (5 mg/week) for a long time, folic acid, curantil (0.125 mg x 2 times daily), captopril (4 mg x 3 times daily), cardonate, panangin, topically – phonophoresis with hydrocortisone on foci, electrophoresis with lipase, local therapy (ointment "Locoid"), massage of scleroderma foci.

Follow-up of the child for 6 months showed improvement in general condition, increased motor activity, appetite, mood, positive changes in scleroderma foci on the legs (softening of the affected areas, the ability to fold the skin, the appearance of fat in these places), positive dynamics of echocardiographic parameters.

Discussion. This clinical case demonstrates one of the variants of JSS course with severe heart lesion in a young child. In the cardiology clinic a pronounced dilatation of the left ventricular cavity with a significant decrease in systolic function – ejection fraction of 25%, mitral regurgitation and open oval window (according to echocardiography) was revealed. Laboratory studies did not reveal any changes in clinical blood tests, increase in biochemical, acute phase findings. In diagnostically insignificant titers of antinuclear factor, there was an increase in antibodies to the specific scleroderma-specific antigen Robert, which is represented by a polypeptide weighing 52 kDa (Ro-52), and an increase in blood concentrations of Ig A, M, G, E. Ultrahigh N-terminal propeptide of natriuretic hormone (NT-pro-BNP) – 10500 ng/ml, with positive dynamics against the background of treatment after 2 months – 4157 ng/ml (norm up to 125) were characteristic.

Dilated cardiomyopathy – heart muscle disease that develops as a result of genetic predisposition, chronic viral myocarditis, immune system disorders. Researchers adhere to the polyetiological hypothesis

of disease development. There are idiopathic, familial (or genetic), viral (and/or immune) and dilated cardiomyopathy, associated with known cardiovascular diseases, characterized by dilatation of the heart chambers and systolic dysfunction of the left ventricle in the absence of severe hypertrophy of the heart. (hypertension, valve defects) or coronary heart disease, which can cause global deterioration of systolic function [9]; and it was diagnosed in our patient. Cases of dilated cardiomyopathy are described, which are the result of various pathological processes and are often secondary to the underlying pathology, which is characterized by damage to the heart muscle, as exemplified by this clinical case. Therefore, it is important to timely establish the correct diagnosis and the underlying cause that led to heart lesion with the subsequent appointment of appropriate therapy, this has a positive impact on the further course of the disease and the quality of life of the child.

In the modern literature we have not found clear data that would indicate the development of dilated cardiomyopathy in juvenile sclerosis. Although, based on the pathogenesis of the disease, it is theoretically possible as a result of impaired microcirculation, vasculopathy of small vessels such as obliterating endarteritis, cardiomyocyte fibrosis. The lack of a sufficient number of controlled studies determines the difficulties of early diagnosis and pharmacological therapy of children with systemic sclerosis. Treatment is selected according to the individual needs of the patient, based on the specific clinical manifestations of the disease and complications of the organs involved.

The Research Group on Systemic Sclerosis in the UK presented a consensus on the management of heart disease in systemic scleroderma [13], which noted that shortness of breath, palpitations, decreased exercise tolerance, dizziness, fainting, chest pain, orthopnoe, increased fatigue and peripheral edema should alert the physician as for the possibility of heart disease. Patients with these symptoms should have regular (every 6 months) comprehensive cardio-respiratory monitoring in a multidisciplinary group that includes both rheumatologists and cardiologists. The consensus also presents new evidence of the association of NT-proBNP with cardiac lesions in systemic scleroderma [13], although its prognostic value is unknown. NT-proBNP, as a diagnostic biomarker of heart lesion was significant in our young patient in the onset and in the dynamics of the disease. Therefore, in order to potentially detect early heart involvement and monitor the patient's condition, we can recommend a baseline measurement of NT-pro BNP and its monitoring in patients with systemic sclerosis.

CONCLUSIONS

1. The presented clinical case demonstrates the features of the onset of juvenile sclerosis in young children with a burdened hereditary history of autoimmune pathology (psoriasis in father and grandmother), which are characterized by widespread progression of the autoimmune process with skin lesions and severe pathology. non-compact (dilated) cardiomyopathy with the development of heart failure.
2. Early detection of cardiovascular damage using modern diagnostic methods, timely adequate therapy in a multidisciplinary team and regular cardiovascular screening can improve prognosis, quality of life and reduce mortality in this category of patients.

Conflict of interest. The authors declare no conflict of interest.

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