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DIFFICULTIES IN SYSTEMIC SCLEROSIS DIAGNOSIS ON THE EXAMPLE OF CLINICAL CASE

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A clinical case of middle-age female patient diagnosed with systemic sclerosis with lesions of skin, joints, vessels, gastrointestinal and respiratory systems. The disease manifested with Raynaud phenomenon, due to this patient was consulted by different specialists but the diagnosis of systemic sclerosis was made 5 years after its onset. This clinical case illustrates the features of the clinical course of systemic sclerosis and difficulties in timely diagnosis of this disease.

KEY WORDS: systemic sclerosis, Raynaud phenomenon, diagnosis difficulties

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INTRODUCTION

Systemic sclerosis (SSc) is a rare chronic systemic disease of the connective tissue, presenting with generalized microangiopathy, immune dysregulation and fibrosis of skin and internal organs [1]. Features of SSc are high level of patient-to-patient clinical variability, multiple organ lesions and a progressive course leading to disability. The incidence of SSc varies from 2.3 to 10 people per 1 million. SSc usually appears in women aged 30–40 years with a female-to-male ratio of 3-6:1[2]. Etiology of SSc is not known. Pathogenesis of SSc is associated with excessive fibrosis, impaired microcirculation and the immune system dysregulation. An imbalance of cellular and humoral immunity is characteristic of SSc, leading to the activation of the synthesis of interleukins IL-1, IL-4, IL-6 and specific antinuclear antibodies (anticentromere antibodies, anti-Scl-70), antibodies to endothelium and connective tissue [3]. The main forms of systemic sclerosis are [3, 4]:

1. Diffuse systemic sclerosis(dSSc) – involves skin thickening of the trunk and the extremities proximal to the elbows and knees besides involvement of the face;

2. Limited systemic sclerosis (lSSc) – affects areas distal to the elbows and knees and also may involve the face and neck;

3. Systemic sclerosis sine scleroderma (ssSSc) – there is internal organ involvement in the absence of clinically apparent cutaneous involvement;

The manifestation of SSc often begins with Raynaud phenomenon (RP), which in 70 % of cases is the first clinical sign of SSc [1, 4]. The progression of RP leads to ischemic-trophic disorders: the formation of ulcers, as well as osteolysis. Skin lesions are specific for SSc and are divided into 3 phases: edematous, indurative and atrophic. Characteristic features of SSc are: mask-like face with radial furrowing around the mouth, skin tightening and tension, as well as sclerodactyly which is a hardening of the skin of the hands with increasing limitation of movements and the development of contractures [5]. The gastrointestinal tract lesions (dysphagia, gastroesophageal reflux disease) as well as the respiratory (pulmonary hypertension, interstitial lung fibrosis), renal (renal crisis, chronic renal failure), cardiovascular (myocardial fibrosis, arrhythmias, heart failure), musculoskeletal (arthralgia, myalgia, arthritis) and genitourinary (erectile dysfunction, bladder fibrosis) systems lesions are frequently involved in systemic sclerosis clinical presentation [4].

Diagnosis of SSc is based on criteria for the classification of systemic sclerosis that include features of clinical presentation (skin changes, RP, pulmonary lesions), serological tests (presence of systemic sclerosis–related autoantibodies), capillaroscopy abnormalities [6]. Treatment of SSc is based on the prescription of antifibrotic drugs (D-penicillamine) in combination with arterial vasodilators, antiplatelet agents, non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, disease-modifying antirheumatic drugs (DMARDs). Therapy of SSc also includes symptomatic treatment depending on the internal organs involvement [7].

OUR CASE

Female 39 years-old patient presented with complaints on pain and swelling of wrists more pronounced at night, lasting up to 5-6 hours, subsiding at rest with stiffness of wrists, inability to perform fine handwork; changing of skin color of hands to pale, then bluish that is aggravated in cold, chilliness and numbness of the hands and feet more pronounced in the cool season (due to this patient has to wear gloves and warm socks all the time); pain in knee and elbow joints with stiffness up to 2 hours. Also complains were of constant feeling of skin tightness especially on the face; inability to open mouth widely; changing of voice; difficulty of swallowing of solid foods, constant heartburn. Patient was concerned about periodical dyspnea on exertion; general weakness, fatigue, decreased muscle strength, hair loss and periodical fever up to 37.5 °C. Patient also noted episodes of painless intermenstrual bleeding.

ANAMNESIS OF THE DISEASE

In year 2008 after childbirth patient first started to experience chilliness and numbness along with paleness and blueness of the fingers of both hands in the cold. She was consulted by district physician but diagnosis was not made and treatment was not prescribed; recommendations were to avoid hypothermia and wear gloves. In 2008–2013 condition of the patient progressively deteriorated, appeared pain in wrists, shoulder, knee, elbow joints, inability to perform fine handwork, difficulty in swallowing of solid food, feeling of skin tightness on the face, hair loss, changing of voice, weight loss. In January 2013 after URVI patient had a pronounced deterioration in her general condition: pain in the joints of the hands became more severe, appeared deep non-healing ulcers on the fingertips. In September 2013 she was consulted by a surgeon with the diagnosis: Felon of the distal phalanx of the left thumb. Due to this patient was treated with antibiotics but without significant effect: full blood count showed significant increase of ESR – 42 mm/hour despite of the antibioticotherapy, the general condition of the patient did not improve. After non-successful treatment the patient was referred to rheumatologist and in October 2013 was admitted to the rheumatology department, where she was diagnosed with systemic sclerosis, stage II (generalized), subacute course, activity II stage, with damage to the skin (edema, induration), blood vessels (Raynaud syndrome, stage III ischemia), joints (polyarthritis with predominant lesions of the hands, wrists, elbow, knee, feet joints, *radiographic* changes of II grade, functional impairment I st.), esophagus (esophagitis). The patient was treated with methylprednisolone (20 mg/day). D-penicillamine was prescribed but the patient refused to use it due to her financial issues. Despite the treatment Raynaud phenomenon progressed and in December 2013 developed an osteolysis of the distal phalanx of the left thumb. Subsequently, the patient had planned hospitalization 2 times per year in a specialized rheumatology department. Takes constantly methylprednisolone, amlodipine, naftidrofuryl, aspirin. Last hospitalization was due to the worsening of the general condition (pain in wrists and cyanosis of the fingers became more pronounced).

ANAMNESIS OF LIFE

Patient is not working due to disability of 3rd degree; denies smoking, alcohol abuse. Postponed diseases: URVI, pneumonia (May 2016); postponed operations: surgical treatment of cataract of both eyes (March 2016). Patient has mensis from 14 years old, also notes episodes of intermenstrual bleeding, which started 1 year ago; due to this she never had doctor's consult. Tuberculosis, diabetes mellitus, viral hepatitis, peptic ulcer, allergic reactions denies. Hereditary history is not burdened.

OBJECTIVE EXAMINATION

General condition of the patient is of moderate severity, clear consciousness, posture

is active. Weight – 50 kg, height – 164 cm. BMI – 18,6 kg/m^2; t – 36.8 °C. Skin is pale, clean, dry, tightened; the patient has mask-like facial features, with poor mimic and radial furrowing around the mouth, incomplete opening of the mouth is observed. There is pallor, cyanosis of the skin of the hands and feet, their swelling, hardening of the skin, hypothermia. On the distal phalanges of the fingers - pitting scaring about 2–4 mm. Mucous membranes: pale-pink, tongue is covered with white plaque; lymphatic nodes are not palpated; peripheral edema is absent. Thyroid gland is not enlarged on palpation. Hoarseness of voice is present. Musculoskeletal system: hypothermia, cyanosis of the fingers; thickening, swelling and induration of the skin of the hands with smoothed contours of the metacarpophalangeal (MCP), carpometacarpal (CMC), wrist joints with pain on palpation, reduced muscular strength up to 3 points, limited flexion to 70 %. There is defect of distal phalanx of the left thumb and pitting scarring of the fingertips. Feet: hypothermia, cyanosis, puffiness, thickening, induration of the skin of the toes, tenderness to palpation. Other joints are not visually altered; there is no soft tissue swelling, change of skin color and skin temperature; slight tenderness on palpation of the knee and elbow joints. Range of movements in the joints is described below (see table 1).

Table 1

Range of movements in joints

Types of movement	Wrist joints	Elbow joints	Knee joints	Ankle joints
Extension /flexion	Right:45/40 Left: 50/40	Right:180/40 Left:175/40	Right:180/40 Left:180/40	Right:60/100 Left:60/110
Normal range (extension/flexion)	65/75	180/40	180/40	70/130

Lungs: resonance percussion sound, on auscultation – harsh breathing over both lung fields, RR -18. Heart borders on percussion are not enlarged, heart tones are clear, loud, rhythmic, HR – 74 bpm; BP – 110/70 on both arms, radial pulse is weakened, synchronous, rhythmic at 74 bpm. Abdomen: epigastric tenderness on palpation; liver is at the costal margin, painless; spleen is not palpable. Tapping sign is negative on both sides. Urination is free, painless.

THE RESULTS OF CURRENT PATIENT'S INVESTIGATIONS

- Full blood count: leukocytosis – 14,8*10^9/L (N – 4,0–9,0*10^9/L); ESR – 17 mm/h (N – 2–15 mm/h); urinalysis – all parameters within the normal range;
- Biochemical panel (fasting plasma glucose, AST, ALT, urea, creatinine, total protein, calcium, potassium, sodium, chlorides, 25(OH)D, CRP, seromucoid) – CRP – 11 mg/l (N < 5), other parameters within the normal range;
- Serological tests: positive ANA (antinuclear antibodies), positive anti-SS-A 52/60 with titer of 6.8 AI (N < 1 AI), anti-Sm/RNP with titer of 8 AI (N < 1 AI), anti-RNP- titer of 8 AI (N < 1 AI); anti-JO-1, anti-dsDNA, anti-Scl70, anti-centromere antibodies were negative;
- ECG: sinus rhythm, HR – 71 bpm, left anterior fascicular block of bundle of Hiss;
- EchoCG: chambers of the heart are not enlarged, myocardial contractility is satisfactory, ejection fraction – 58 %;
- Chest X-ray: in lungs – infiltrative lesions are absent, sinuses of the lungs are without pathological changes, there are signs of pneumofibrosis, size and shape of the heart within normal limits;
- Upper Gl tract radiography: signs of gastroesophageal, duodenogastral reflux, esophagitis, sliding axial hernia of 1st degree;
- Ultrasound of abdominal organs, kidneys: no pathological changes; ultrasound of the pelvic organs: echo signs of endometrial polyp;
- Rheovasography of the vessels of the upper limbs: in the left hand blood supply is reduced by 29 %, mild hypovolemia; in the right hand the blood supply is reduced by 34 %, moderate hypovolemia; the tone of large and medium arteries, the tone of small arteries, arterioles and venules in both hands is normal;
- X-ray of hands: bone defect in the distal phalanx of the left thumb; shortening, fuzziness

of the adjacent interphalangeal joint plates of the left thumb with elements of marginal resorption; cystic restructuring of the heads of the metacarpal bones, patchy osteoporosis of the carpal bones (fig. 1).

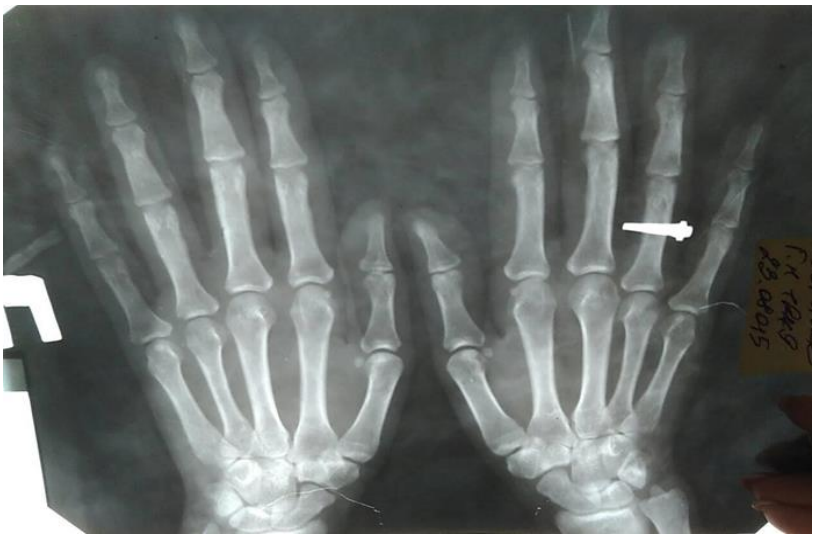

Fig. 1. X-ray of hands.

CONSULTS OF SPECIALISTS

- Consultation of gastroenterologist: gastroesophageal reflux, duodenogastral reflux, esophagitis, sliding axial hiatal hernia of 1st degree.
- Consultation of vascular surgeon: Raynaud syndrome, chronic ischemia of III-rd degree.
- Consultation of gynecologist: endometrial polyp, recommended surgical intervention.

DIAGNOSIS

Main diagnosis: Systemic sclerosis, stage II (generalized), chronic course, activity of stage I, with skin lesions (edema, induration), vessels (Raynaud syndrome, ischemia of III degree), joints (polyarthritis with predominant lesion of the joints of the hands, wrists, feet, *radiographic* changes of II degree, functional impairment of I degree), esophagus (gastroesophageal, duodenogastric reflux, esophagitis, sliding axial hernia of 1 degree), lungs (pneumofibrosis).

Concomitant diagnosis: Polyp of endometrium.

RECOMMENDATIONS AND TREATMENT

Recommendations were to maintain healthy lifestyle, avoid physical overload, overcooling, insolation; diet with limitation of mechanical and chemical irritants, stimulants of gastric secretion, substances that linger for a long time in the stomach. Patient was advised to use moisturizing, emollient hypoallergenic skin care products.

Dynamic observation of specialists was recommended: rheumatologist, vascular surgeon, gastroenterologist, ophthalmologist, gynecologist, pulmonologist.

Drug therapy: methylprednisolone 8 mg per day – constantly under the control of clinical and laboratory activity of the disease; naftidrofuryl hydrogen oxalate 200 mg 3 times a day for 3 months; pentoxifylline 600 mg 1 time per day – 2 months; amlodipine 2.5 mg 1 time a day – continuously under the BP control; aspirin 75 mg after dinner – continuously; omeprazole 20 mg 1 time per day - from the 1st to the 10th day of each month.

Recommendations: spirometry and consultation of pulmonologist; surgical therapy for endometrial polyp: polypectomy.

DISCUSSION

Diagnosis of systemic sclerosis in the early stages has certain difficulties due to the poor specificity of the clinical picture, patients' underestimation of the severity of their condition, as well as low medical awareness for the identification of SSc [8]. According to studies [9], early signs of SSc include puffy, swollen fingers, Raynaud phenomenon, specific microvascular abnormalities by capillaroscopy and the presence of autoantibodies: ANA and

specific for SSc anticentromere and antito-poisomerase-I antibodies. Presence of Raynaud phenomenon and puffy fingers are not often considered by patients as «serious symptoms» requiring a doctor's consultation. Due to research study [8] patients with kidney damage, difficulty breathing and ulcerative lesions of the fingers consulted the doctor almost immediately after the onset of these symptoms, while patients with Raynaud phenomenon sought medical help 6–9 months after the first complaints appeared. An important factor in the early diagnosis of SSc is the level of awareness of doctors, especially general practitioners, who are most often approached by patients with initial manifestations of systemic sclerosis. According to a study with interviewing of rheumatologists, dermatologists and general practitioners in Europe and America [8], it was found that there was low medical awareness for identifying SSc in general practitioners that along with an underestimation of the symptoms by the patients contributed to the late diagnosis of SSc. Another issue for timely diagnosis of SSc is that very early presentation of systemic sclerosis in most of the cases doesn't have sufficient features to fulfill the present classification criteria due to the American College of Rheumatology and European League Against Rheumatism [6, 10, 11].

SSc in our patient manifested in the form of Raynaud's phenomenon, however, during the initial examination, her symptoms were not regarded as signs of a rheumatic disease; further laboratory and instrumental investigations were not performed, which undoubtedly led to a late diagnosis of SSc. The diagnosis of SSc in our clinical case was made 5 years after the onset of the disease, when developed an overt clinical picture with lesions of the joints, blood vessels, gastrointestinal tract, and pronounced specific changes of the skin.

The tendency to the prevalence of late diagnosis of SSc is described by many authors [9, 10, 12-13]. It is obvious that the diagnosis of SSc in the late stages does not carry significant difficulties; mostly due to specific skin changes, as well as multiple organ lesions and vascular disorders [8]. However, the treatment of such patients in the later stages is limited because of: pronounced internal organs involvement, microvascular remodeling, tissue fibrosis or atrophy which are already irreversible [9]. Severe complications of SSc such as renal crisis, interstitial pulmonary fibrosis and pulmonary hypertension, ischemic limb lesions and osteolysis often lead to disability and increased mortality of these patients [4].

While treatment in the early stages of SSc allows to slow down and control the progression of the disease and to prevent irreversible pathological changes and thus avoid the disability of the patients [9, 11, 14]. Despite the fact that early signs of SSc such as Raynaud phenomenon and swollen puffy fingers have low specificity, they were suggested to be considered as «red flags» for a general practitioner, which will allow suspicion of SSc and further serological and instrumental studies aimed at early detection of this disease [11].

CONCLUSIONS

Diagnosis of systemic sclerosis in our patient was made a 5 years after the onset of symptoms mainly due to weak medical vigilance in detection of rare rheumatologic diseases, as a result late diagnosis in this case led to untimely prescribed treatment and to the disability of the patient. An important task for the practicing physician is the ability to recognize the first signs of systemic sclerosis - «red flags», which will help to diagnose the disease at early stages, start timely treatment to prevent irreversible pathological changes, early disability and mortality of patients with SSc.

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СКЛАДНОСТІ У ДІАГНОСТИЦІ СИСТЕМНОЇ СКЛЕРОДЕРМІЇ НА ПРИКЛАДІ КЛІНІЧНОГО ВИПАДКУ

Голубкіна Є. О., Сіленко І. Ю., Брахмбхатт Х.

Представлено клінічний випадок системної склеродермії з ураженням шкіри, суглобів, судин, шлунково-кишкового тракту і дихальної системи у пацієнтки середнього віку. Захворювання маніфестувало у вигляді феномена Рейно; в зв'язку з цим пацієнтка зверталася до різних спеціалістів, однак діагноз системної склеродермії був поставлений через 5 років після початку хвороби. Цей клінічний випадок ілюструє особливості клінічного перебігу системної склеродермії та складності своєчасної діагностики цього захворювання.

КЛЮЧОВІ СЛОВА: системна склеродермія, феномен Рейно, складності діагностики

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СЛОЖНОСТИ В ДИАГНОСТИКЕ СИСТЕМНОЙ СКЛЕРОДЕРМИИ НА ПРИМЕРЕ КЛИНИЧЕСКОГО СЛУЧАЯ

Голубкина Е. А., Силенко И. Ю., Брахмбхатт Х.

Представлен клинический случай системной склеродермии с поражением кожи, суставов, сосудов, желудочно-кишечного тракта и дыхательной системы у пациентки среднего возраста. Заболевание манифестировало в виде феномена Рейно; в связи с этим пациентка обращалась к разным специалистам, однако диагноз системной склеродермии был поставлен через 5 лет после начала болезни. Этот клинический случай иллюстрирует особенности клинического течения системной склеродермии сложности своевременной диагностики этого заболевания.

КЛЮЧЕВЫЕ СЛОВА: системная склеродермия, феномен Рейно, сложности диагностики

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