DOI: 10.20514/2226-6704-2021-11-1-72-75

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ОЦЕНКА ЭФФЕКТИВНОСТИ ЛЕЧЕНИЯ РИТУКСИМАБОМ ПРИ СИСТЕМНОЙ СКЛЕРОДЕРМИИ (КЛИНИЧЕСКИЙ СЛУЧАЙ)

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Evaluation of the Efficiency of Treatment with Rituximab for Systemic Scleroderma (A Case Report)

Резюме

В статье описан клинический случай прогрессирующей формы системной склеродермии у мужчины 39 лет. У пациента наблюдалось острое течение и быстрое прогрессирование заболевания со значительным исходным снижением форсированной жизненной ёмкости легких; с признаками неблагоприятного прогноза, такими как диффузная форма, высокий кожный счет (>14 по Rodnan), мужской пол, высокая позитивность по антителам к Scl-70 (антитела к топоизомеразе I). В связи с неэффективностью стандартной терапии глюкокортикоидами и иммуносупрессантами на ранней стадии болезни был рассмотрен вариант лечения генно-инженерными препаратами (ритуксимабом). В результате проводимой терапии отмечена положительная динамика.

Ключевые слова: *системная склеродермия, ритуксимаб, неблагоприятный прогноз*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

Статья получена 15.10.2020 г.

Принята к публикации 11.11.2020 г.

Для цитирования: Харламова Е.Н., Карпенко Ю.Ю. ОЦЕНКА ЭФФЕКТИВНОСТИ ЛЕЧЕНИЯ РИТУКСИМАБОМ ПРИ СИСТЕМНОЙ СКЛЕРОДЕРМИИ (КЛИНИЧЕСКИЙ СЛУЧАЙ). Архивъ внутренней медицины. 2020; 10(6): 72-75. DOI: 10.20514/2226-6704-2021-11-1-72-75

Abstract

The article describes a clinical case of a progressive form of systemic scleroderma in a 39-year-old man. The patient has an acute course and rapid progression of the disease with a significant initial decrease in the forced vital capacity of the lungs, with signs of an unfavorable prognosis, such as a diffuse form, a high skin count (> 14), male sex, and high positivity for antibodies to Scl-70. In connection with the ineffectiveness of standard therapy with glucocorticoids and immunosuppressants at an early stage of the disease, the option of treatment with genetically engineered drugs (rituximab) was considered. As a result of the therapy, a positive trend was noted.

Key words: *systemic scleroderma, rituximab, poor prognosis*

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Conflict of interests
The authors declare that this study, its theme, subject and content do not affect competing interests

Sources of funding
The authors declare no funding for this study

Article received on 15.10.2020
Accepted for publication on 11.11.2020

For citation: Harlamova E.N., Karpenko Ju.Ju. Evaluation of the Efficiency of Treatment with Rituximab for Systemic Scleroderma (A Case Report). The Russian Archives of Internal Medicine. 2020; 10(6): 72-75. DOI: 10.20514/2226-6704-2021-11-1-72-75

ANF — antinuclear factor, GC — glucocorticoids, GEBT — genetically engineered biologic therapy, ILD — interstitial lung disease, RTM — rituximab, SSc — systemic sclerosis

Relevance

Systemic sclerosis (SSc) is a chronic autoimmune disease that affects the skin, joints and internal organs (heart, lungs, kidneys, digestive tract); it includes immune system and microcirculation disorders, inflammatory changes, and generalized fibrosis. Lung injury is a very common manifestation of SSc. The frequency of pulmonary localization of the sclerotic process is 65–80% [1]. Interstitial lung disease (ILD) in systemic sclerosis is characterized by inflammation in alveoli with excessive proliferation of fibroblasts in the interalveolar septa, vascular walls, perivascular, peribronchial, subpleural and basal areas. ILD contributes to poor prognosis and is the leading cause of mortality in SSc. The treatment of patients with ILD associated with SSc has not been sufficiently studied. A number of studies demonstrate the effectiveness of monoclonal antibodies against B cells (rituximab) [2]. The significance of B cells in SSc pathogenesis is well known: they intensify fibrosis due to the production of fibroblast-activating autoantibodies; B cells can also directly intensify fibrosis by direct intercellular contacts with fibroblasts, and via cytokines (interleukin-6) [3]. Studies show that rituximab (RTM) can improve lung function and reduce the severity of skin fibrosis in patients with SSc [4].

Objective of the study: description of a clinical case with a progressive form of systemic sclerosis that is refractory to standard treatment with glucocorticoids and immunosuppressants.

Materials and methods

A retrospective analysis of the medical record of a patient with systemic sclerosis was carried out.

Male patient, 39, with a diffuse form of systemic sclerosis, with a rapidly progressing course, high activity, with lesions of the skin (hyperpigmentation, sclerodactyly), blood vessels (Raynaud syndrome of upper and lower limbs, auricle necrosis, small digital ulcers), joints (polyarthritis of hands, X-ray stage III, periarticular fibrosis with the formation of contractures), lungs (basal pulmonary sclerosis), gastrointestinal tract (esophageal hypotension, esophageal stricture 0.8–0.9 cm), muscles (history of myositis), heart (myocarditis with rhythm disorders, atrial fibrillation paroxysms, painless myocardial ischemia, chronic heart failure stage 1, FC 1), kidneys (proteinuria), immune disorders (antibodies against topoisomerase I (Scl-70) "+++", antinuclear antibodies (ANF "+") in combination with secondary osteoarthritis of knee joints (X-ray stage I), feet (X-ray stage II). Duodenal peptic ulcer without exacerbation.

At the time of examination (15 Sep 2020), the patient complained of pain in the small joints of hands, dense swelling of fingers, the lower third of forearms, feet, the lower third of lower legs, limited hand mobility, numbness in fingers, whitening and blueing of hands, small ulcers on the tips of fingers and toes, muscle pain, and occasional loose stools.

Medical history: The patient considers himself sick from the beginning of September 2016, when the swelling of ankle joints appeared, then pains in hand joints, elbows, knees, muscles of hips, whitening and blueing of fingers, general weakness, morning stiffness in joints for about an hour. Examination revealed increased acute-phase parameters: C-reactive protein — 10.73 mg/l (normal to 5 mg/l); immunological parameters: ANF "+", AT Scl-70 "+++". The presence of Scl-70 antibodies indicates a diffuse form of disease, a rapidly progressive course and a high risk of severe ILD.

The patient received the following treatment in the Rheumatology Department of the City Hospital: pulse therapy with glucocorticoids (GC) (methylprednisolone 1,000 mg), vascular treatment, immunosuppressive treatment (methotrexate 10 mg/week). The treatment had a short-term effect. From 14 to 31 August 2017, the patient was hospitalized in the Rheumatology Department of the Regional Hospital for disease progression and no effect of treatment. The following therapy was carried out: prostanoids for intravenous administration (iloprost), GC (prednisolone 10 mg), calcium antagonists, pentoxifylline, nonsteroidal anti-inflammatory drugs with slight positive changes. Recommendations included prednisolone with dose reduction from 10 to 5 mg/day,

cyclophosphamide 50 mg/day, PDE5 inhibitor (sildenafil). In December 2017, the patient's condition worsened, muscle and joint pains increased, which required the use of narcotic analgesics for pain relief. The patient was referred to the V. A. Nasonova Federal State Budgetary Research Institution "Research Institute of Rheumatology" (Moscow) to get medical advice in order to determine further treatment strategy. It was recommended to start genetically engineered biologic therapy (GEBT) with rituximab due to the ineffectiveness of standard therapy with GC and immunosuppressants; at the early stage (first 3 years of disease) with signs of poor prognosis, such as the diffuse form, high skin score (> 14 according to the Rodnan scale), male gender, rapid progression with a significant initial decrease in forced lung capacity; high positivity of antibodies against Scl-70.

Combined use of rituximab with GC and mycophenolate mofetil was recommended.

Treatment with rituximab (500 mg) was started in December 2017. Subsequently, RTM infusions (500 mg) were performed every three months. Planned infusion in March 2020 was delayed due to the unfavorable epidemiological situation associated with novel coronavirus disease; infusion was performed in June, the next one is scheduled for late September.

The last hospitalization in the Rheumatology Department was in November 2019.

The patient regularly takes methylprednisolone (8 mg/day), mycophenolate mofetil (2,000 mg/day), antiplatelet agents, angiotensin-converting enzyme inhibitors (perindopril), mineralcorticoid receptor antagonists, calcium antagonists (diltiazem), proton pump inhibitors, non-steroidal anti-inflammatory drugs if necessary.

Patient's life history: No family history of rheumatological diseases. Comorbidities: duodenal peptic ulcer (at the age of 19), fracture of the forearm and left calcaneus, concussion during childhood. Unremarkable history of allergies. Denies contracting tuberculosis, hepatitis B, C, HIV, typhoid, paratyphoid, diabetes mellitus, psoriasis, and cancer. No blood transfusions performed. Denies smoking and drinking alcohol. No contact with infectious patients. Person with group 2 disability since 2016.

Objectively: General condition of the patient is satisfactory. The state of consciousness was normal. Normosthenic body type. Undernourished (height 182 cm, weight 54 kg, body mass index 16 kg/m^2)). Skin with foci of "salt and pepper" hyperpigmentation. Visible mucosae of normal color. Dense swelling of hands, feet, lower third of lower legs, lower third of forearms. Digital ulcer on the thumb (large), healing ones — on 4 fingers of the right hand, on the distal finger of the left hand, on the first toe of the left foot. Muscles are developed satisfactorily, with normal tone. Lymph nodes are not enlarged.

Respiratory system: normosthenic form of the chest. Respiratory rate 16 per minute. No shortness of breath during exercise. Auscultatively: vesicular breathing in lungs throughout all pulmonary fields, somewhat weakened in the lower parts on both sides, no rales.

Circulatory system: heart area with no visible abnormalities. Apex beat in 5 intercostal space along the left midclavicular line. Relative heart dullness: right — along the right edge of sternum, left — along the left midclavicular line, upper — rib 3. Heart sounds are muffled, no murmurs heard. Cardiac rhythm is abnormal, with heart rate of 80 pm. Blood pressure 130/90 mm Hg.

Digestive system: lips of normal color. Tongue is dry, covered with white fur. No visible peristalsis. Tone of abdominal muscles is normal. Abdomen is soft and nontender. Liver is palpated along the edge of costal arch. Spleen is not enlarged.

Urinary system: no swelling in kidney area. Costovertebral angle tenderness was absent on both sides. Stool with a tendency to loose, urination — according to the patient, within normal.

Joint condition: movement in fingers is limited due to swelling and contractures. Palpation of paravertebral points of lumbosacral spine is painless. Palpation of knee joints is moderately painful.

Laboratory test results:

Complete blood count from 04 Sep 2020: hemoglobin 159 g/l, RBC 4.4×10^{12}/l, WBC 5.9×10^{9}/l, platelets 302×10^{9}/l, ESR 7 mm/h. C-reactive protein — negative.

Blood biochemistry on 04 Sep 2020: glucose 4.80 mmol/l, alanine aminotransferase 19 U/l, aspartate aminotransferase 19 U/l, creatinine 79.0 μmol/l, total cholesterol 4.3 mmol/l, total protein 77 g/l, urea 5.0 mmol/l, uric acid 203.0 μmol/l.

Common urinalysis on 04 Sep 2020: color — straw-yellow, transparency — slightly turbid, reaction — acidic, specific gravity 1010, protein — negative, WBC — 1–2 per field of vision.

Immunogram on 28 Nov 2019: immunoglobulin G > 24.000 mg/ml (4.8–16.0 mg), immunoglobulin M 2.200 mg/ml (0.48–2.0 mg), rheumatoid factor 10.6 IU/ml (less than 15), anticentromere antibodies (ACA) 0.1 U/ml (0–10), antibodies against Scl-70 more than 200 U/ml (0.0–25.0).

Diagnostic test results:

Electrocardiogram on 25 Oct 2019: sinus rhythm. Complete left bundle branch block. LV hypertrophy with changes in myocardium of posterolateral wall. Supraventricular extrasystole, ventricular extrasystole. Heart rate 75 bpm. QRS axis in horizontal position.

Echocardiography on 27 Nov 2019: dilated left heart chambers. Aorta, cusps of aortic and mitral valves (MV) are indurated. MV regurgitation grade 1. LV contractile function is reduced (Teicholz EF 51%).

Computed tomography of the chest on 20 Aug 2020: signs of diffuse changes in lungs — pulmonary sclerosis, pulmonary fibrosis, emphysema, calcifications in both

lung apices. Pattern of chronic obstructive pulmonary disease.

Pulmonary function test on 28 Aug 2019: lung capacity and bronchial patency within normal.

Abdominal ultrasound on 18 Dec 2018: signs of moderate diffuse changes in the liver.

Ultrasound of the kidneys on 17 May 2019: no abnormalities were revealed.

X-ray of the hands on 21 Jan 2019: osteoarthrosis grade III.

X-ray of the feet on 21 May 2019: osteoarthrosis grade II, polyarthritis grade I.

Chronometry of esophagus on 18 Dec 2018: barium passing through the esophagus is slowed down. Incompetence of cardia, gastroesophageal reflux. Esophageal hypotension.

Discussion

In response to well-tolerated therapy with rituximab, the patient's condition after three years was stable, disease activity decreased. The clinical picture showed decreased joint pain, decreased skin density, no dyspnea during exercise. According to laboratory tests, the following positive changes are observed: ESR decreased to 7 mm/h, C-reactive protein is negative, hemoglobin level increased to 157 g/l. Spirometry parameters stabilized: lung capacity and bronchial patency within normal. However, severe Raynaud syndrome persists.

Standard treatment with immunosuppressants that is currently used is not effective enough to improve the prognosis of SSc. Therefore, the task of studying and adopting new approaches to treatment remains relevant [5]. Since B-cells are highly significant in SSc pathogenesis, they should be considered as a high-potential therapeutic target. Some clinicians regard RTM as an alternative to immunosuppressants for the management of ILD, and 69% of Canadian SSc experts share this opinion [6]. The latest Russian clinical recommendations concerning SSc also note the advisability of using RTM when standard treatment with immunosuppressants is ineffective or impossible [7].

Conclusions

This clinical observation demonstrates the advisability of prescribing RTM, especially at the early stages of the disease. However, further study of using RTM in controlled trials is required.

Вклад авторов:

Все авторы внесли существенный вклад в подготовку работы, прочли и одобрили финальную версию статьи перед публикацией

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Author Contribution:

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

E.N. Harlamova (ORCID ID: https://orcid.org/0000-0001-8864-7623): contribution to the development of the concept and design, the author's role in the collection, analysis and interpretation of data, the author's consent to be responsible for all aspects of the work

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