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Применение внутривенного иммуноглобулина в терапии рефрактерного дерматомиозита: клиническое наблюдение

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АННОТАЦИЯ

Введение. Дерматомиозит относится к редким аутоиммунным заболеваниям. Его развитие часто ассоциировано со злокачественными солидными опухолями. В связи с полиморфностью клинических проявлений и низкой информированностью врачей первичного звена о данном заболевании дерматомиозит длительное время остается недиагностированным, что приводит к позднему началу лечения. Несвоевременное начало терапии ассоциировано с плохим прогнозом для этой группы пациентов. К факторам неблагоприятного прогноза относят развитие и прогрессирование дисфагии, а также рефрактерность к стандартной терапии системными глюкокортикоидами (сГК) и иммунодепрессантами. В таком случае возникает необходимость применять альтернативные методы терапии, в т. ч. внутривенный иммуноглобулин (ВВИГ).

Цель. Продемонстрировать клинический случай дерматомиозита, резистентный к терапии высокими дозами сГК и метотрексатом, потребовавший применения высокодозной терапии ВВИГ.

Представлено клиническое наблюдение дерматомиозита у пациентки С., 56 лет, с кожным синдромом и мышечной слабостью, дисфагией и дисфонией. На фоне терапии преднизолоном 1 мг/кг в сутки внутрь, метотрексатом 15 мг в неделю подкожно клинико-лабораторная динамика незначительная, плохая переносимость метотрексата не позволяла повысить его дозу. Учитывая нарастающую дисфагию, врачебная комиссия приняла решение о проведении высокодозной терапии ВВИГ в дозе 1 г/кг однократно. Через 4 недели терапии отмечалась отчетливая положительная клинико-лабораторная динамика.

Заключение. Описанный клинический случай продемонстрировал эффективность и безопасность применения ВВИГ для лечения рефрактерного дерматомиозита при недостаточной эффективности предшествовавшей стандартной терапии сГК и иммунодепрессантами.

Ключевые слова: *дерматомиозит; воспалительная миопатия; внутривенный иммуноглобулин; папулы Готтрона; гелиотропная сыпь*

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Use of Intravenous Immunoglobulin in Treatment for Refractory Dermatomyositis: a Case Report

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ABSTRACT

INTRODUCTION: Dermatomyositis is a rare autoimmune disease. Its development is often associated with malignant solid tumors. Due to the polymorphism of clinical manifestations and low awareness of the primary care physicians of this disease, dermatomyositis remains undiagnosed for a long time, which leads to a late start of treatment. Untimely start of treatment is associated with a poor prognosis for this group of patients. Factors of poor prognosis include the development and progression of dysphagia and also refractoriness to the standard therapy with systemic glucocorticoids (sGC) and immunosuppressants, when it becomes necessary to use alternative methods of treatment, including intravenous immunoglobulin (IVIG).

AIM: Demonstration of a clinical case of dermatomyositis resistant to high-dose sGC and methotrexate therapy, that required high-dose IVIG therapy.

A clinical case of dermatomyositis in a female patient S., 56 years old, with cutaneous syndrome and muscle weakness, dysphagia and dysphonia is presented. On treatment with prednisolone 1 mg/kg a day orally, methotrexate 15 mg a week subcutaneously, clinical and laboratory dynamics was insignificant, poor tolerance to methotrexate did not permit to increase the dose. Taking into account progressing dysphagia, the medical commission took a decision about high-dose IVIG treatment at a dose 1g/kg once. After four weeks of therapy, clear positive clinical and laboratory dynamics was noted.

CONCLUSION: The described clinical case demonstrated the effectiveness and safety of IVIG for treatment of refractory dermatomyositis with insufficient effectiveness of the previous standard therapy with sGC and immune depressants.

Keywords: *dermatomyositis; inflammatory myopathy; intravenous immunoglobulin; Gottron papules; heliotrope rash*

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ECO•VECTOR

LIST OF ABBREVIATIONS

ALT — alanine aminotransferase
AST – aspartate aminotransferase
CPK — creatine phosphokinase
IVIG — intravenous immunoglobulin
MMT8 — Manual Muscle Testing 8
sGC — systemic glucocorticoids
US — ultrasound examination

INTRODUCTION

Modern medicine pays great attention to diseases of the musculoskeletal system, the prevalence of which has tended to increase in recent years, one of which is dermatomyositis, a rare autoimmune disease that belongs to the group of inflammatory myopathies [1, 2]. Dermatomyositis is a rare autoimmune disease that belongs to a group of inflammatory myopathies. The basis of pathogenesis is myositis leading to a widespread necrosis of muscle tissue, and, as a result, to a multiple increase in the level of creatine phosphokinase (CPK) in blood serum, a marker of necrosis of myocytes. Morphologically, lymphohystiocytic infiltration of myocytes is determined as a manifestation of autoimmune inflammation and necrotized muscle fibers [3]. Skin biopsy in dermatomyositis is characterized by hyperkeratosis, epidermal atrophy, basement membrane thickening, dermal edema, mucin deposit and perivascular infiltration with CD4+ lymphocytes [4]. Besides, in skin biopsy, damage to endothelial cells and dilation of skin vessels may be noted.

The clinical picture is dominated by the cutaneous syndrome, which usually includes heliotrope rash, periorbital edema, ulcerations, Gottron papules and signs of damage to striated and smooth muscles [5]. Due to the presence of a pronounced cutaneous syndrome, which often precedes muscle damage by several months, such individuals may become patients of dermatologists with a high degree of probability. Later, the clinical presentation of the disease changes, proximal muscle weakness and characteristic laboratory findings add to the cutaneous syndrome. Such patients become unclear for the primary care physicians, which leads to late diagnosis and untimely start of treatment.

The prevalence of dermatomyositis ranges from 1 to 7 cases per 100 thousand population [6, 7]. Women are affected approximately twice more often than men, especially in the age group over fifty years. Epidemiological studies have shown the association between inflammatory myopathies and malignant neoplasms with the higher risk of detection of the latter than in the population of the respective age groups [7–9]. The frequency of malignant neoplasms in inflammatory myopathies makes 9.0% to 50.0%, the association with malignant neoplasms has been described for all types of myopathies, but they are most often identified in dermatomyositis [10]. Dermatomyositis is associated with solid tumors cancer of cervix, ovaries, mammary gland, bladder, lungs, pancreas, stomach. On identification of the patient with dermatomyositis, he is subjected to examination for probable oncopathology.

The prognosis for life and further ability to work in this disease depends on the timeliness of the diagnosis and initiation of treatment. Risk factors for an unfavorable prognosis are advanced age of the patient, swallowing disorders, interstitial lung disease, the presence of severe somatic diseases, chronic foci of infection, and late initiation of treatment.

The clinical picture of the disease is determined by a characteristic cutaneous syndrome and involvement of muscles. Manifestations of the cutaneous syndrome include Gottron papules, ‘spectacles symptom’, a typical sign of dermatomyositis is peeling and cracks in the skin of the palms and fingers, in the area of the periungual folds, the so-called ‘mechanic's hand’ or ‘washerwoman's hand’. Besides, a typical damage to the periungual folds is edema and erythema [11, 12]. Muscle damage is manifested by weakness of the proximal group of muscles of the shoulder and pelvic girdle, spontaneous falls due to sudden weakness in the muscles of the lower limbs [13]. With further progression of the disease, the muscles of the pharynx and esophagus become involved in the pathological process, and there is a risk of developing aspiration complications, which can potentially be the cause of an unfavorable prognosis [14, 15].

The diagnosis of the disease is based on the patient examination data, results of laboratory and instrumental examination. To confirm the diagnosis, of much importance is determination of the level of myositis-associated enzymes in the blood serum: CPK, aspartate aminotransferase (AST), alanine aminotransferase (ALT),

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aldolase. Idiopathic dermatomyositis is characterized by detection of myositis-specific and myositis-associated antibodies in the blood serum: anti-Jo-1-antibodies, anti-Mi-2-antibodies, in case of the overlapping syndrome, anti-PM/Scl-antibodies may be detected.

Of the instrumental methods, the most diagnostically significant are needle electromyography, magnetic resonance imaging of muscles, and muscle biopsy. Capillaroscopy may also be useful in diagnostics, especially in the case of overlapping syndrome. In this case, thrombosis of the nail bed capillaries and capillaritis are detected [16].

Inflammatory myopathies in most cases demonstrate a good therapeutic and laboratory response to systemic glucocorticoids (sGC) in high doses, and to immunosuppressants (methotrexate, azathioprine, cyclophosphamide). A complete or partial response to the use of sGC in an adequate dose can be achieved in 75.0%–90.0% of patients with inflammatory myopathies, which is manifested by a buildup of muscle force and normalization of CPK level.

In a number of clinical cases, refractoriness to the standard treatment is noted, which has a poor prognostic value, since inflammation that is not eliminated for a long time, leads to involution of muscle tissue to connective tissue. In this case, further anti-inflammatory therapy becomes unreasonable because of the absence of inflammatory substrate and development of generalized fibrosis [17].

In the treatment of refractory myositis, genetically engineered biological drugs with different mechanism of action can be used [18]. Thus, 25.0%–53.0% of physicians give preference to tumor necrosis factor α inhibitors, 19.0%–44.0% prefer rituximab, 11.0% abatacept, and there are single cases of use of anakinra.

In case of severe refractory myositis, when high doses of sGC and immunosuppressants appear ineffective, high-dose therapy with intravenous immunoglobulin (IVIG) can be used to relieve a long-standing sluggish inflammation in myocytes. Besides, an indication for IVIG in inflammatory myopathies is the presence of severe dysphagia [19].

The literature describes a limited number of cases of the use of IVIG in dermatomyositis. The largest randomized placebo-controlled study was performed by a team of authors led by R. Aggarwal (2022) [20]. The study involved 95 patients (47 patients received IVIG therapy, 48 people — placebo group), the diagnosis of dermatomyositis was established according to Bohan and Peter criteria. The study included patients who had previously received treatment with sGC or other immunosuppressants (methotrexate, azathioprine, mycophenolate mofetil, sulfasalazine, leflunomide, tacrolimus, ciclosporin, hydroxychloroquine), and the therapy was ineffective, or side effects from the therapy were noted. The maximum allowable dose of sGC at the beginning of the study was 20 mg/day in prednisolone equivalent, the dose remained unchanged throughout the study period. A comprehensive assessment of dermatomyositis activity was performed: Manual Muscle Testing (MMT8) score, total disease activity assessment, patient global assessment of disease activity, health status questionnaire, and serum muscle enzyme levels (CPK, AST, ALT, and aldolase).

IVIG was administered at a dose of 2 g/kg every 4 weeks for 16 weeks. By week 16 of treatment, 79% of patients in the IVIG group had a total MMT8 score improvement at least 20. Overall, after 16 weeks of IVIG treatment, the percentage of improvement was significantly higher among those receiving IVIG than among those receiving placebo. Tolerability of IVIG therapy was assessed. The most common adverse events were headache (42.0% of patients), hyperthermia (19.0% of patients), nausea (16.0% of patients), 9 cases of serious adverse events were recorded, including 6 thromboembolic events.

The **aim** of this study to demonstrate a clinical case of dermatomyositis resistant to therapy with high doses of systemic glucocorticoids and methotrexate, which required the use of high-dose intravenous immunoglobulin therapy.

Case Report

A female patient S., 56 years old, was admitted to the rheumatology department of the Regional Clinical Hospital of Ryazan with ***complaints*** of pain, weakness in the muscles of hips and shoulders, in the muscles of neck, difficulty rising arms and getting up from the bed. Areas of redness on the skin of face, limbs, torso. The appearance of ulcerative defects on the skin of the upper hips. Difficulty swallowing, choking when taking food, nasal accent.

From the ***history***, symptoms appeared about 6 months before, when the patient noted areas of redness on the skin of the upper and lower limbs, abdomen, chest, face. Then pain appeared in the muscles of the shoulder girdle, neck, hips. The patient repeatedly consulted a dermatologist, but the diagnosis remained unclear. After 6 months, she consulted a rheumatologist and was hospitalized in the rheumatology department with suspected dermatomyositis.

On ***examination***, the patient's condition was satisfactory. Body mass index 30.5 kg/m^2. Clear consciousness. The lymph nodes not enlarged. Visible mucous membranes clean. Vesicular breathing, no rales, respiratory rate 18 per minute. Heart sounds muffled. Rhythm regular, heart rate 74 per minute, blood pressure 140/90 mm Hg. The tongue moist, free swallowing. Abdomen soft, painless to palpation. Liver not enlarged; spleen not palpable. Stool 1 time a day.

Pasternatsky symptom negative on both sides. Urination free, painless.

Areas of erythema on the skin of the face in the area of the nasolabial folds, chin — heliotrope rash. Erythema with edema around the eyes of 'dermatomyositis glasses' type (Figure 1). Areas of erythema on the skin of the upper limbs, chest, abdomen, hips. 'V-shaped' erythema on the skin of the chest in the décolleté area, on the skin of the back of a 'shawl' type, symmetrical atrophic scars in the area of the upper third of the upper arms (Figure 2). Symmetrical ulcerative defects on the skin of the upper third of the thighs the 'holster' symptom (Figure 3). Dryness and cracks in the area of the periungual folds 'mechanic's hand', Gottron papules in the area of the proximal interphalangeal, metacarpophalangeal joints of the hands (Figure 4).

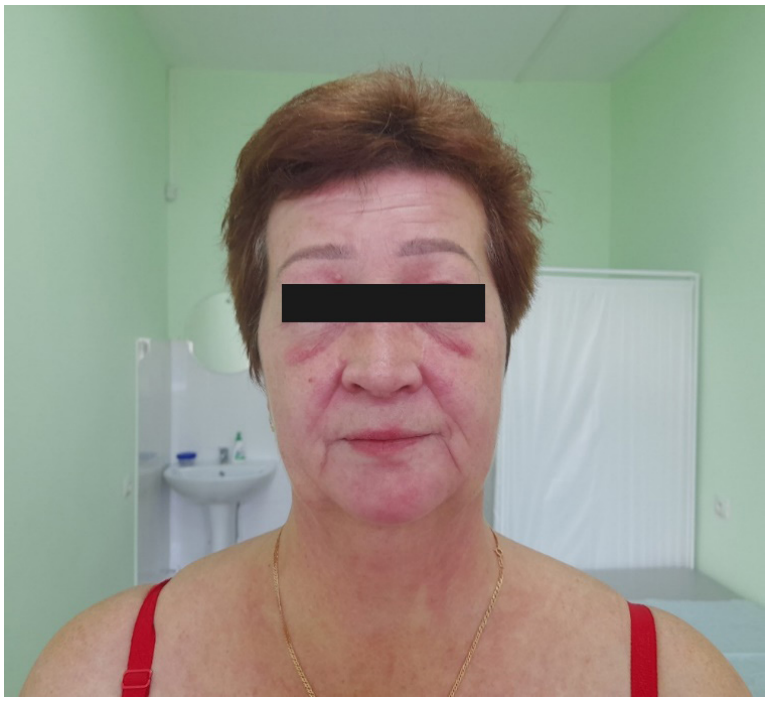

Fig. 1. Heliotrope rash on the face, 'dermatomyositis glasses'.

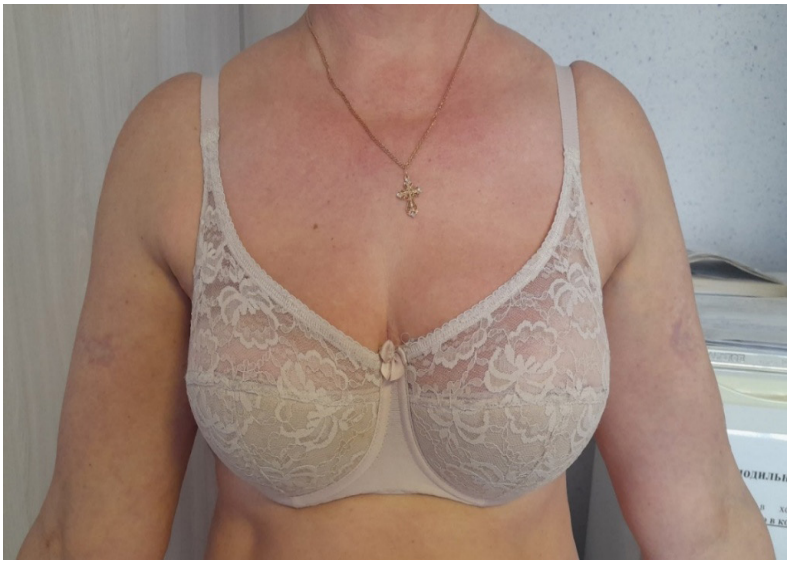

Fig. 2. 'V-shaped' erythema on the skin of the chest in the décolleté area, symmetrical atrophic scars in the upper third of the shoulders.

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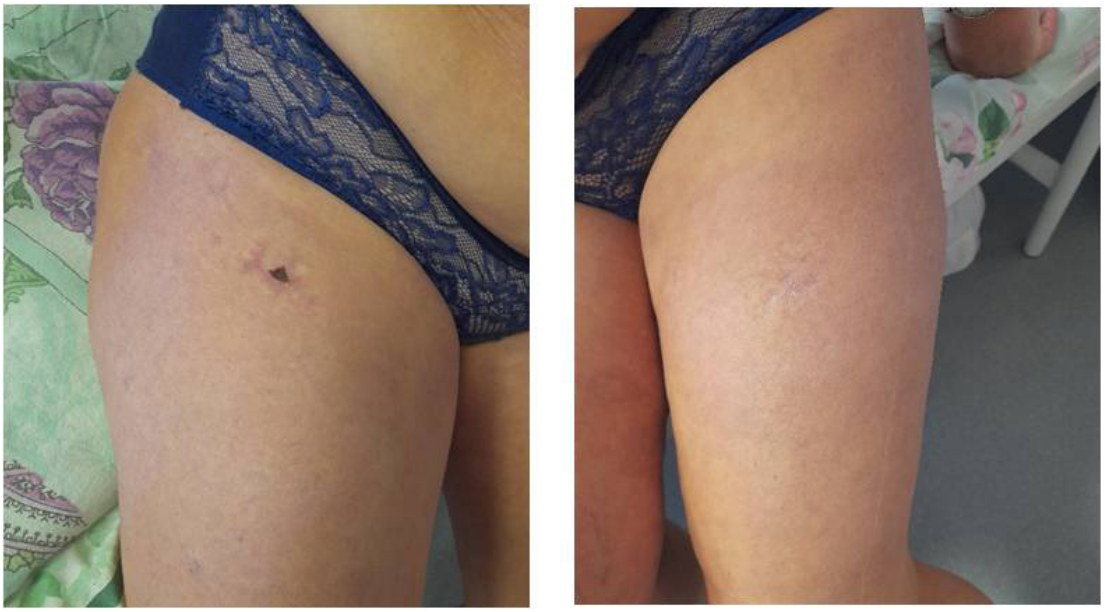

Fig. 3. Symmetrical ulcerative defects on the skin of the upper third of the thighs.

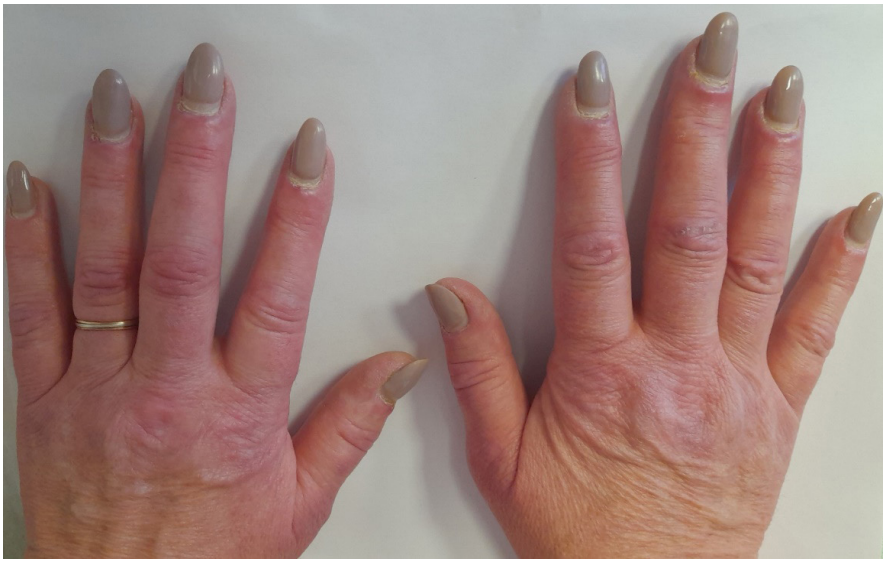

Fig. 4. Periungual erythema, 'mechanic's hand', Gottron papules.

On palpation, painfulness of the muscles of the shoulder and pelvic girdle was noted. Weakness in the muscles of the shoulder and pelvic girdle. The manual muscle testing MMT8 score was 22 points.

Below, the results of laboratory and instrumental examination are presented.

Clinical blood test: erythrocytes 4.68 × 10^{12}/l, hemoglobin 136 g/l, leukocytes 14.1 × 10^{9}/l, platelets 234 × 10^{9}/l, erythrocyte sedimentation rate 10 mm/h according to Westergren.

Biochemical blood test revealed an increase in myositis-associated enzymes, typical for inflammatory myopathy: CPK 4116 U/l (reference values 10 U/l–195 U/l), AST 208 U/l (reference values 8 U/l–48 U/l), ALT 152 U/l (reference values 7 U/l–45 U/l).

An ***immunological examination*** was performed to detect myositis-specific and myositis-associated autoantibodies (anti-Jo-1, anti-Mi-2, SRP, anti-RNP,

anti-Scl70, anticentromere antibodies, antibodies to Smith antigen, anti-Ro (SSA), anti-La (SSB) antibodies): not detected.

Given the presence of active cutaneous syndrome, an examination was performed to exclude systemic lupus erythematosus: a blood test for antibodies to native double-stranded deoxyribonucleic acid 1.8 IU/ml (reference values less than 20 IU/ml), a blood test for the C3 complement component 1.1 g/l (reference values 0.82 g/l–1.85 g/l), C4 complement component 0.26 g/l (reference values 0.15 g/l–0.53 g/l). Taking into account the presented results, no data for systemic lupus erythematosus were found.

Electrocardiogram: sinus rhythm, vertical position of the electrical axis of the heart.

Electroneuromyography of the upper and lower limbs: signs of primary muscle damage. Conduction along the motor fibers of the examined nerves not impaired.

X-ray of the hands, X-ray of the metatarsus and phalanges of the toes: without pathology.

An examination was conducted to exclude the presence of a malignant neoplasm and damage to internal organs in a systemic disease of connective tissue. No specific changes were detected on echocardiography, X-ray computed tomography of the chest organs, ultrasound examination (US) of the mammary glands, US of the pelvic organs, fibrogastroduodenoscopy, US of the abdominal organs.

US of thyroid gland: the structure of both lobes was deranged by multiple heterogeneous hypoechoic masses on the right and single ones on the left, probably of colloidal nature. In the left lobe closer to the upper pole, an isoechoic mass containing a liquid component was localized, with sharp even contours, measuring 14.7 × 9.5 × 16 mm. In the projection of the left lobe node an active stromal and peripheral blood flow. Conclusion: focal masses of both thyroid lobes of colloidal nature. The left lobe nodule according to the *Thyroid Imaging Reporting and Data System IV* (TI-RADS IV).

Taking into account the presence of a TI-RADS IV category node of the left thyroid lobe in the patient with dermatomyositis, a puncture thin-needle aspiration biopsy under US control was recommended. A cytological examination of the obtained material confirmed benign follicular character of the node. The patient was examined by an ***endocrinologist***, and the diagnosis of multinodular euthyroid goiter was established.

Given the presence of dysphagia and dysphonia, the patient was consulted by an ***otolaryngologist***: oropharyngeal dysphagia. X-ray of the nasal sinuses: without pathology.

Based on the clinical picture of the disease, examination data, the ***clinical diagnosis*** was established:

Underlying disease: primary idiopathic dermatomyositis with involvement of the muscles of the shoulder and pelvic girdle (proximal muscle weakness), oropharyngeal dysphagia, dysphonia, cutaneous lesion (heliotrope rash, Gottron papules, 'mechanic's hand', ulceration), elevated levels of myositis-associated enzymes. *Associated disease:* multinodular euthyroid goiter.

Therapy was prescribed: prednisolone 1 mg/kg per day orally, methotrexate 15 mg per week subcutaneously. On the treatment, the patient's condition showed slight positive dynamics, slight decrease of pain in the muscles of the shoulder and pelvic girdle, increase in the proximal muscle strength the patient began to stand up on her own, hold her head up. Positive laboratory dynamics was noted in terms of decrease in the level of myositis-associated enzymes after 3 weeks of therapy: CPK 1254 U/l, AST 142 U/l, ALT 126 U/l. However, choking during food intake became more frequent. The patient did not tolerate methotrexate therapy well, nausea was noted, and therefore increasing methotrexate dose was not possible. In view of the increasing dysphagia, high-dose IVIG therapy was administered once at a dose of 1 g/kg. The drug was prescribed off-label by a medical commission, the patient's voluntary informed consent for the use of this type of therapy was obtained. The therapy was tolerated satisfactorily, with no serious infusion reactions. After 4 weeks of therapy, a positive dynamic of clinical and laboratory data was noted. Weakness in the limbs decreased, the patient stopped choking while eating. Cutaneous manifestations decreased: cutaneous hyperemia, epithelialization of he ulceration sites occurred. Positive dynamics of the level of myositis-associated enzymes were noted: CPK 856 U/l, AST 83 U/l, ALT 76 U/l.

On discharge from the hospital, consultation with oncologist, endocrinologist was recommended in dynamics, continuation of prednisolone 1 mg/kg orally for 2–3 months. After normalization of AST, ALT, CPK gradual decrease in prednisolone dose to the supporting level (not more than 10 mg a day), methotrexate 15 mg a week subcutaneously, folic acid 5 mg a week, gastroprotection using proton pump inhibitors, osteoporosis prevention (calcium preparations at a dose of 1,000 mg a day, cholecalciferol 2,000 IU daily). Dynamic observation by a rheumatologist.

During prospective observation, ulcerative defects on the skin of thighs epithelialized with formation of atrophic scars of irregular shape in their place. Heliotrope rash completely stopped after 4-month treatment. The level of myositis-associated enzymes normalized after 6 months of therapy. After 12 months of follow-up there were no complaints of pain in muscles of the limbs, mild non-permanent weakness persisted in the lower limbs, the manual muscle testing MMT8 score was 34 points.

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DISCUSSION

IVIG can produce a pro-inflammatory effect when appointed in low doses and anti-inflammatory effect in high doses. The pro-inflammatory effect of low doses consists in activation of complement components. High doses of IVIG are used for treatment of autoimmune inflammatory diseases. The anti-inflammatory effect of high doses of IVIG is realized through blockade of C3 and C4 complement components and reduction of complement function, reduction of synthesis of T-cell lymphokines (interleukins, tumor necrosis factor), enhancement of apoptosis of B-lymphocyte and reduction of antibody synthesis [19, 21].

More than 150 cases of use of IVIG for rheumatologic and neurologic indications are reported in 6781 patients participating in clinical trials and 362 patients in individual cases. Refractory forms of inflammatory myopathies are additional indications for the administration of high-dose IVIG therapy [22].

The effectiveness of IVIG in therapy for inflammatory myopathies was demonstrated in individual clinical observations and pilot studies. Having analyzed the results of these studies, S. S. Nikitin and L. M. Boriskina came to the conclusion about the effectiveness of IVIG in 66% of patients with inflammatory myopathies, which was expressed in the increase in muscle strength, disappearance of cutaneous lesions, and normalization of enzyme levels [23]. Indications for administration of IVIG in this group of patients were the insufficient effect of sGC and immunosuppressants, repeated impairment of the condition despite the use of standard therapy in adequate doses. The first signs of clinical improvement were noted at 2 weeks after the start of treatment, significant clinical improvement was noted after the 2nd or 3rd course of IVIG. Clinical and laboratory improvement persisted on average for a year and was confirmed by prospective observations. Positive dynamics of symptoms was confirmed by the results of repeated biopsy of a skin-muscle flap. With high-dose IVIG therapy, an increase in the diameter of muscle fibers, a decrease in complement deposits in capillaries, and a decrease in the diameter of capillaries were noted [22]. IVIG therapy is well tolerated (in the conducted studies, no significant adverse drug reactions were noted) and has a steroid-sparing effect [24].

Scientific publications describe various IVIG therapy regimens for resistant dermatomyositis. E. A. Aseeva and S. K. Soloviev recommend using IVIG at a dose of 1 g/kg for 3–5 consecutive days and then monthly until the effect is achieved [22]. Alternative IVIG regimens are also found in the literature: 2 g/kg for 2–5 days once a month until the effect is achieved [22, 23]. The use of IVIG in the treatment of children and adolescents with juvenile dermatomyositis seems promising due to the minimal side effects of this type of therapy compared to cytostatics. In children, IVIG is used according to the regimen of 1 g/kg for 2 consecutive days once a month or 1 g/kg–2 g/kg per day 1–2 days every 2 weeks for 3 months, then once a month for two years [25].

When discussing the given clinical case, it should be noted that at the onset of the disease, the patient developed a classic cutaneous syndrome, characteristics of dermatomyositis. It preceded the clinical signs of the damage to the striated and smooth muscles by several months, which is consistent with the literature data [3]. However, because of low awareness of the primary care physicians and dermatologists about this pathology, the patient was referred to a rheumatologist only 6 months after the onset of disease. According to the literature, late start of pathogenetic therapy is a poor prognostic factor for this group of patients and can lead to insufficient effectiveness of the prescribed therapy and refractory course of dermatomyositis [11, 12], which was what happened in this clinical case. The patient was admitted to the rheumatology department with dysphagia and dysphonia, progressive muscle weakness. Thus, the indication for the use of high-dose IVIG therapy in this clinical case was refractoriness to the standard therapy with sGC and methotrexate, the presence of progressive dysphagia. According to the literature, repeated courses of IVIG are usually required to achieve a clinical and laboratory effect, signs of clinical improvement are observed 2 weeks after the start of therapy, significant clinical improvement is noted after the 2nd or 3rd course of IVIG [23]. In this observation, we used one course of IVIG with a good clinical and laboratory response. Currently, the duration of follow-up is 5 years, clinical and laboratory remission is maintained with use of supporting therapy with methotrexate, no relapses of the disease were noted.

Taking into account a high oncologic alertness in this group of patients, patient S. underwent oncologic screening. During the examination of the patient, a node of the left lobe of thyroid of TI-RADS IV category was detected; the biopsy results did not confirm malignancy of the formation. However, given a high probability of oncopathology in this group of patients, repeat US of thyroid at 3 months, consultation with an oncologist [26], and further annual oncologic screening were recommended [27].

CONCLUSION

This clinical case is of interest due to the existence of the classic cutaneous syndrome in a patient, characteristic of dermatomyositis, in combination with striated and smooth muscle damage.

On therapy with systemic glucocorticoids and methotrexate, an insufficient clinical and laboratory

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response was noted, severity of dysphagia increased, for which reason high-dose therapy with intravenous immunoglobulin was recommended.

After the intravenous introduction of immunoglobulin, a gradual relief of cutaneous manifestations of dermatomyositis, increase in muscle strength and normalization of swallowing and voice were noted. Positive clinical dynamics was confirmed by the results of laboratory examinations and gradual normalization of the level of myositis-associated enzymes.

ADDITIONALLY

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