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RESEARCH ARTICLE

An Integrated Approach to the Treatment of Severe Psoriasis: A Clinical Case

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Abstract

Psoriasis is a disease of autoimmune origin, affecting not only the skin, but also the internal organs of a person. Currently, many methods of treating psoriasis are in use, which vary in effectiveness. The aim of this work is to analyze the results of complex physiotherapeutic and pharmacological treatment of a patient with severe psoriasis in comparison with the initial failed treatment with traditional pharmacological methods**.** The therapy was carried out in 2018-2019 (observation by a rheumatologist at the place of residence), after treatment that was unsuccessfully carried out in 2016 at the Institute of Rheumatology (Federal State Budget Scientific Institution "Scientific Research Institute of Rheumatology named after VA Nasonova") with an incorrect diagnosis of rheumatoid arthritis. In the secondary complex therapy, the following treatment methods were used: a) antihistamines (Chloropyramine 1.0 IM in the evening for 22 days, Chloropyramine 1 tablet 2 times a day in the morning, 18 days for the day); b) Methotrexate 15 mg IM once a week; c) hepatoprotector (heptor 400 mg 1 tablet 1 time per day-22 days); d) Folic acid 0.1 mg 2t 2 pd -6 days; e) Desensitizing therapy (200 ml of 0.9% Sodium Chloride-20 days); f) Local therapy (Komfoderm; Salicyl-dermatol ointment-22 days); g) Physiotherapeutic methods. With complex treatment, the trunk skin showed rashes regression, up to residual hyperpigmentation. The rash regression was 50% in the form of a decrease in the brightness of erythema in the palms, a decrease in peeling and the number of papular elements. Similar processes occurred on the skin of the feet, but with the preservation of large-plate peeling. A detailed literature analysis of known methods of treatment of psoriasis, with a comparison of new and traditional methods was performed. In recent years, the treatment of psoriasis has become more focused on targeted biological drugs. New methods of treatment not only demonstrate optimistic results, but also lead to a deeper understanding of the immunopathogenetic pathways of psoriasis, identifying new potential targets for therapeutic intervention and diagnosis. Our comprehensive approach has allowed us to establish one of the ways to achieve effective treatment.

Key words: *Psoriasis, Pharmacology, Symmetry, Paradoxical reaction, Physiotherapy, Papules, Rashes, peeling of the skin.*

Introduction

Psoriasis is a chronic inflammatory disease of an autoimmune nature, mediated by T cells, characterized by damage not only to the skin in the form of psoriatic plaques, but also to other organs, the severity and course of which varies from patient to patient. The disease can manifest at any age, but most often its onset is fixed at the age of 15 to 25 years (Benoit & Hamm, [1]. In addition, psoriasis occurs in children, accounting for an average of 4% in the overall structure of dermatological pathology in children under the age of 16 years [2].

In the world, the psoriasis incidence is approximately 2-4% [3]. In Russia, this indicator also varies depending on the territory - from 0.72 to 11.8% [4]. At present, psoriasis (Ps) is considered as a systemic immunoassociated disease of a multifactorial nature with a dominant value in the development of genetic factors, characterized by accelerated proliferation of epidermocytes and a violation of their differentiation, immune reactions in the dermis and synovial membranes, an imbalance between pro-

inflammatory and anti-inflammatory cytokines, chemokines; frequent pathological changes in the musculoskeletal system [5]. Psoriasis and PsA are considered as T-cell-mediated diseases in which persistent inflammation occurs associated with overproduction and an imbalance of key pro- and anti-inflammatory cytokines, such as tumor necrosis factor α (TNF-α), interleukins 12/23, 17, 6, etc. The main cells in the development of psoriasis are dendritic cells (DC), T helper cells (Th) 1 and 17, and keratinocytes. Activated by various DC signals, they produce and secrete tumor necrosis factor (TNF) alpha and interleukins (IL). IL23 induces the differentiation of naive T cells into Th17.

Activated Th17 produce excessive amounts of IL17 and IL22. TNF-α and IL17 activate keratinocytes, cause epidermal hyperplasia, activate inflammatory cells, such as neutrophils, and also induce additional production of antimicrobial peptides (AMPs). DC-secreted IL12 also activates Th1, which produce cytokines, including interferon (IFN) gamma.

This immune response is enhanced by subsequent activation of DC by TNF-α. An association of psoriasis with the HLA-C*0602 allele encoding the HLA-Cw6 molecule has also been identified. In the pathogenesis of PsA, the leading role is played by hyperproduction of pro-inflammatory cytokines, in particular tumor necrosis factor alpha (TNF-α), which ultimately determines the heterogeneity of the clinical manifestations of PsA [6].TNF-α is a cytokine involved in the formation of the inflammatory process and regulates the growth, survival and function of the cells of the immune system [7].

TNF-α can induce apoptosis, trigger inflammation, inhibit carcinogenesis and viral replication. TNF-α plays an important role is in the pathogenesis of rheumatic inflammation, since it triggers a cascade of inflammatory and destructive processes in which osteoclasts, synovial fibroblasts and chondrocytes are involved, which leads to the development of pain, edema, the formation of bone erosion and narrowing of the joint gap. Thus, TNF-α causes both hyperproliferation of keratinocytes, leading to the development of skin psoriatic changes, activates leukocytes, stimulates the proliferation of blood vessels in the microvasculature, the pathogenetic mechanisms of psoriasis and PsA [8]. Therefore, by blocking TNF-α, we stop the development of inflammatory processes. The diagnosis of PsA is established based on the identification of characteristic clinical and radiological signs of the disease.

In recent years, TNF-α inhibitors, one of the first classes of genetically engineered biological agents (GEBA), have shown significant efficacy in the treatment of psoriasis and PsA. In the Russian Federation, the following drugs of the class of TNF-α inhibitors were registered for the treatment of PsA: etanercept, adalimumab, infliximab, certolizumab and golimumab, which, as noted above, reduce not only the activity of the inflammatory process in the joints, spine, skin joints and skin, but also delay the destruction of joints, reduce the frequency of metabolic and cardiovascular complications in patients with PsA [7].

Despite the significant GEBA effectiveness in various inflammatory immune-dependent pathologies, in a number of patients, however, the expected effect cannot be achieved due to the presence of primary and secondary inefficiency, the development of side effects.

Monoclonal antibodies are known to possess antigenic properties, as they are protein molecules that contain both mouse and human protein and thereby cause the formation of human antimere antibodies - human antichimeric antibodies (HACA). However, there are completely human (non-foreign protein) monoclonal antibodies that have low immunogenicity, and thus have high efficiency and safety. However, human anti-human antibodies can be formed against human monoclonal antibodies (human anti-human antibodies - HAHA).

Thus, different representatives of the class of TNFα inhibitors have different immunogenicity, which should be taken into account when prescribing drugs and evaluating their effectiveness [9].TNF-α inhibitors are recommended for PsA patients with active peripheral arthritis who do not achieve remission or minimal disease activity during treatment with methotrexate or other disease-modifying anti-rheumatic drug (DMAR) for ≥ 3-6 months, as well as in the presence or appearance of joint erosion

despite taking DMAR [5].CZP (Simzia drug, manufactured by UCB Pharma, SA, Belgium, the active ingredient certolizumab pegol) is a polyethylene glycol (PEG), i.e. a pegylated, antigen-binding (Fab) fragment of a monoclonal antibody that neutralizes soluble and membrane-associated TNFα. CZP is unique in its structure, since binding to PEG lengthens the half-life of CZP, and the drug accumulates mainly in inflamed tissues, which also refers to the effects of pegylation.

All this provides a fast onset and long-term effect of the drug. In addition, pegylation has a "masking effect", which means a decrease in the drug immunogenicity, since a small percentage of antibodies to the drug is detected [10]. CZP was registered for the treatment of PsA in 2014.To date; the data is accumulated about drugs that cause manifestation (de novo) or exacerbation of psoriasis. For such drugs as ß-blockers, lithium preparations, antimalarial drugs, interferons, imichimod and terbinafine, an association with psoriasis has been proven [11].

Recently, evidence of exacerbation of psoriasis was found during treatment with genetically engineered biological therapy drugs, the so-called unusual - paradoxical - adverse reactions (AR) that resulted from the treatment of diseases with genetically engineered biological drugs. The first reports of psoriasis associated with treatment with TNF-α inhibitors appeared in 2003. At the moment, many different methods listed above are used in the treatment of psoriasis, but all of them give results that differ in their effectiveness. In our article, we attempt to compare traditional methods of treatment and the methods of physiotherapy we have applied comprehensively, treatment with antihistamines and hepatoprotective drugs along with drugs used in the treatment of psoriasis itself.

A clinical case is considered, an analysis of the reasons for successful therapy is carried out. The authors hypothesized that the combined use of pharmacology and physiotherapy can lead to remission and cure even in patients with severe psoriasis. The aim of this work is to carry out complex therapy for a patient with severe psoriasis against the background of an initially failed treatment with traditional methods.

Material and Methods

Clinical Observation

Patient, born in 1977, considers herself a patient from the age of 11, when she first noticed the appearance of rashes of the "dandruff" type on the scalp. Repeatedly consulted with doctors, but not diagnosed with Psoriasis. Use of various topical agents with a moderate positive effect was recommended. Patient was noted a significant improvement in the summer.

In September 2016, she was admitted to the Institute of Rheumatology (Federal State Budget Scientific Institution "Scientific Research Institute of Rheumatology named after VA Nasonova") with complaints of pain in the knee joints, small joints of the feet and hands. Diagnosis: "Rheumatoid arthritis, seropositive, anti-CCP-positive." For the first time, the diagnosis of psoriatic arthritis is suspected, since on the skin of the scalp in the frontotemporal areas a congestive erythema and mid-plate peeling with white scales were noted.

Therapies

Primary Therapy in 2016 with a Diagnosis of Rheumatoid Arthritis

Methotrexate therapy was carried out 10 mg/week, Arcoxia 90 mg - with a positive effect on the part of the joint system. In August 2017, the dose of Methotrexate was increased to 20 mg/week, due to insufficient effect. Given the high clinical and laboratory activity of the disease, in October 2018 monotherapy with TNF-α Symzia inhibitor was prescribed, according to the scheme of 6 courses of 2 injections of 200 mg of the drug with an interval of 2 weeks.

After the 5th course, exacerbation of psoriasis of the scalp progresses over the next 2 months with reading into the process of the skin of the palms and feet. By the end of the 3rd month, rashes spread throughout the skin. Due to the severity of the skin process, she was hospitalized at the Sechenov University Dermatological Hospital (Clinic of Skin and Venereal Diseases VA Rakhmanov) for complex treatment. In January 2019, pronounced negative dynamics were noted: the skin process became chronic in inflammatory. The rash was plentiful, symmetrical.

The process affected the scalp, trunk, most densely located on the skin of the palms and soles. On the skin of the body, rashes were represented by multiple papular and pustular elements 0.5-0.7 cm in diameter, rounded outlines, dense texture, merging into plaques up to 4-5 cm in size.

On the feet there were multiple pustules with a size of 0.5 cm or more, with serous and hemorrhagic contents merging into larger bubbles, there was a large-plate peeling and areas of pronounced hyperkeratosis (Fig. 1A).

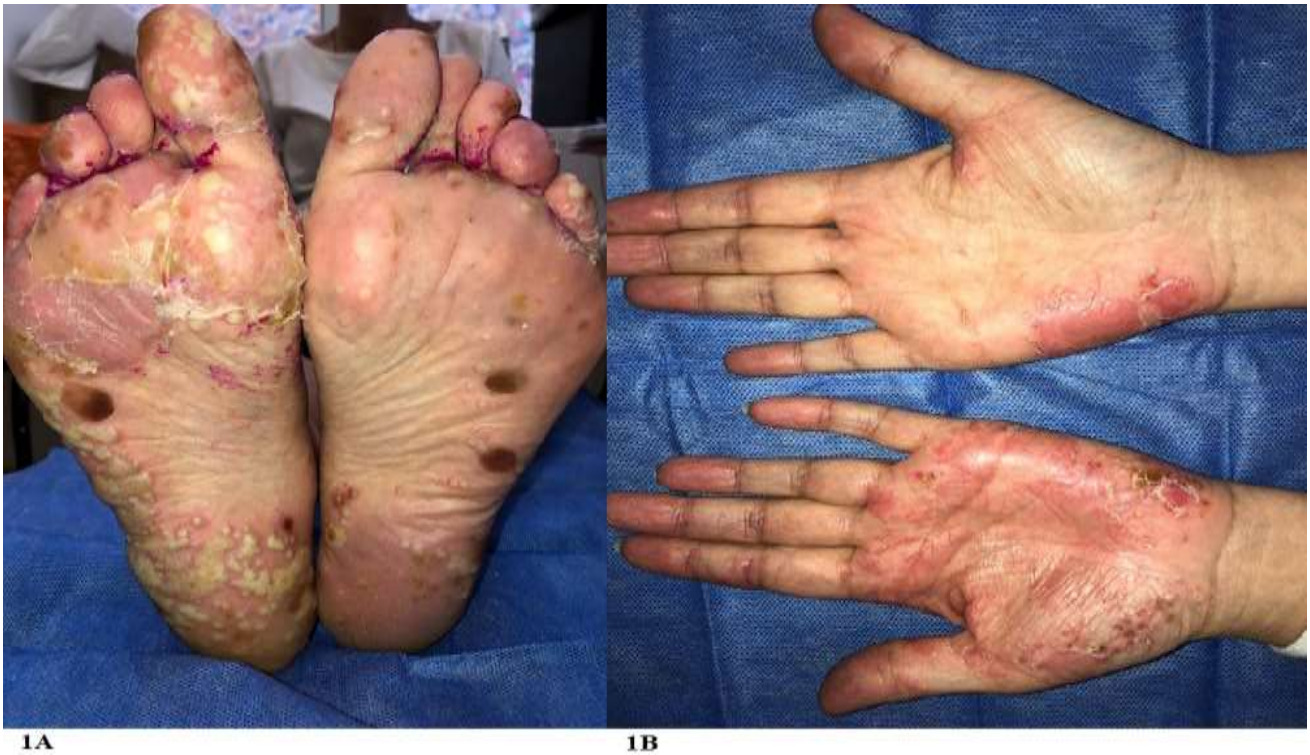

Figure 1: The patient's condition before treatment: hyperkeratosis on the feet (1A) and papules on the palms (1B)
On the palmar surfaces there are multiple papules, merging into plaques up to 2 cm in size of rounded shape, of dense consistency (Fig. 1B). Subjective: moderate skin itching. the appearance of rashes on the skin of the palms and soles in the form of pustular elements. Due to the severity of the skin process, she applied to Clinic of skin and venereal diseases named after V.A. Rakhmanov for complex therapy

Histological Examination

A histological examination of a skin biopsy reveals cavities filled with polymorphonuclear leukocytes in combination with the spongiosis of the surrounding epidermis.

Results

Results of the Initial Examination in the Department

General condition: moderate. Consciousness: clear. Mental state: not changed; Position: active; Body temperature: 37°C. Height: 164cm. Weight: 55kg. BMI: 20.45kg/m^2. Build: normosthenic. Skin: color: normal. Characteristics: rashes. Humidity: dry. Visible mucous membranes: normal color. Nails: not changed. Subcutaneous fat development: moderate. Distribution: uniform. Mammary glands: without features. Swelling: no. Lymph nodes: not palpable; The muscular system is developed: good. Tone: normal.

Osteoarticular system: There is visible deformation of the joints. Endocrine system: Thirst: None. Appetite: normal. Finger tremor: no. Eyelids tremor: no. Tongue tremor: no. Body hair: according to the female type. Thyroid: not enlarged; Shtellwag's sign: no. Gref sign: no. Moebius sign: no. Marie sign: no. Respiratory system: Nasal breathing: free; both nostrils passable.

Dry nose: no. Nasal discharge: no; No pain; Independent: no; With pressure and striking: no. Voice: clean. Shape of the chest: conical. Chest asymmetry: no; The position of the blades on the same level: yes; Shoulders: lay tightly to the chest. Auxiliary respiratory muscles involved in breathing: no. Type of breath: mixed. BR in minutes: 16. Breathing rhythm: correct; Palpation of the chest: painless; Voice trembling on the symmetrical sections of the chest is carried out: the same.

Both halves participate in the act of breathing: evenly. Comparative lung percussion: a clear pulmonary sound is heard

over the entire surface. Auscultatory: respiration: vesicular. Auscultatory: wheezing: no. Auscultation: crepitation: no. Pleural friction noise: no. Bronchophony: the same on both sides not changed. Circulatory system. Inspection of the vessels of the neck: vessels of the neck are not changed. Veins: not swollen. Vein ripple: no. Carotid arteries ripple: yes. Examination of the heart area: cardiac hump: no. Cardiac impulse: not determined; Apical impulse visually: not determined; Palpation: determined; not reinforced.

Ripple in the epigastric region: no; Heart configuration: normal. Heart sounds: rhythmic. Pulse: rhythmic. Filling: satisfactory. Voltage: satisfactory. Auscultation of the heart: heart sounds are clean, rhythmic. Pericardial rub: no. BP on the right hand, mmHg: 120/80. BP on the left hand, mmHg: 120/80. Ripple of peripheral vessels: saved. Condition of the veins: satisfactory. Digestive organs. Appetite: good. Aversion to food: no; Intestinal activity: stool: regular; Once a day: 1; Chews food: good. Swallowing and passage of food: free. Oral cavity: smell: absent; Mucous: regular color; Gums: pink; Tongue: wet; clean;

Teeth: sanitized. Inspection of the abdomen: without visible pathological changes. Varicose veins of the anterior abdominal wall: none; Ascites: no. Postoperative scars: no. Percussion of the abdomen: tympanitis. Superficial palpation: painless. Deep palpation: painless. Liver. Edge of the liver: rounded. Liver surface: smooth. Liver consistency: soft elastic. Soreness: b/b. Gall bladder: not palpable.

Palpation at the point of the gallbladder: not painful. Ortner sign: no. Murphy's sign: no. Frenicus sign: no. Vasilenko sign: no. Mussey sign: no. Courvoisier sign: no. Projection area of the pancreas during palpation: painless. Mayo-Robson sign: None. Grotto sign: no. Shofar sign: no. Urinary organs. Urination: free; Intermittent stream: no; Rapid: no; Abundant: no. Pain during urination: no.

Low back pain: none. Pain behind: no. Kidneys: not palpable. Symptom of lumbar effusion: negative. Soreness in the ureteric points: painless. Palpation of the kidneys: painless. Percussion and palpation of the bladder: painless.

Local status. The skin process is a chronic inflammatory in nature. The rash is plentiful, symmetrical.

The process affects the scalp, trunk, most densely located on the skin of the palms and soles.

Rashes are represented by multiple papular and pustular elements 0.5-0.7 cm in diameter, rounded outlines, dense consistency, merging into plaques up to 4-5 cm in size. On the feet there are multiple pustules of 0.5 cm or more in size, with serous and hemorrhagic contents, merging between themselves into larger bubbles, there is a large-plate peeling and areas of pronounced hyperkeratosis. On the palmar surfaces there are multiple papules. Merging into plaques. Up to 2 cm in size of rounded shape, dense consistency. Subjective: moderate skin itching.

Laboratory Test Data

Biochemical analysis of blood dated 15.02.2019: Urea nitrogen: 2.7 mmol/l; Albumin: 43.3 g/l; AST: 21 units/l; Total protein: 68.8 g/l; Total bilirubin: 13.2 µmol/l; Total bilirubin: 13.2 µmol/l; Direct bilirubin: 3.8 µmol/l; GGT: 6 units/l; Glucose: 4.9 mmol/l; Iron: 25.5 µmol/l; LDH: 345 units/l; Triglycerides: 1.1 mmol/l; Cholesterol: 5.28 mmol/l; Alkaline phosphatase: 178 units/l;

Biochemical analysis of blood dated 01.03.2019: ALT: 15 units/l; Albumin: 43.4 g/l; AST: 32 units/l; Total protein: 70.8 g/l; Bilirubin total: 12 µmol/l; GGT: 6 units/l; Alkaline phosphatase: 181 units/l; Coagulogram dated 15.02.2019: prothrombin % according to Quick: 93%; APTT: 0.95 Ratio; INR: 1.05; Fibrinogen: 4.02 g/l;

Complete blood count dated 15.02.2019: HCT: 38.6%; HGB: 132 g/l; MCH: 31.7 pg; MCHC: 342 g/l; MCV: 92.7 fl; PLT: 301 10*9/l; RBC: 4.16 10*12/l; RDW: 12.9%; WBC: 10.4 10*9/l; Basophils%: 0.4%; Lymphocytes #: 2.6 10*9/l; Lymphocytes%: 25.3%; Monocytes #: 1 10*9/l; Monocytes%: 9.3%; Neutrophils #: 6.3 10*9/l; Neutrophils%: 60.7%; Unclassified%: 1.6%; ESR: 16; Color Index: 0.95; Eosinophils #: 0.3 10*9/l; Eosinophils%: 2.7%.

Specialist Consultations

Consultation with a physiotherapist in a hospital (Consultation with a

physiotherapist) dated 18.02.2019: Conclusion: Due to the severity and torpidity of the process, a course of narrow-band therapy UVB-311nm was started according to the method of 4 single exposure per week (initial dose of UVB radiation - 0.1 J/cm2) in combination with local PUVA therapy on the palms and soles with a 0.3% solution of amifurin. There are no contraindications to treatment. Consultation of a physiotherapist in a hospital (Consultation of a physiotherapist) from 27..2019: Conclusion: patient received 7 sessions of narrow-band therapy UVB-311nm and 7 sessions of local PUVA therapy.

The treatment is well tolerated. On the part of the skin process, improvement is noted. The exposure mode is the same. Consultation of a rheumatologist from 28.02.19: conclusion: The patient has increased psoriasis, the spread of foci on the scalp, palmar-plantar psoriasis with TNF (Symzia). Considering intolerance to the drug, a change to Tofacitinib (Yakvinus) 5 mg is indicated 2 times a day - for a long time, in combination with Methotrexate (METoject) 25 mg/week (folic acid use).

Treatment Performed

- Antihistamines (Chlorpiramine 1.0 in the evening in the evening - 22 days, Chlorpiramine 1 tablet 2 times a day in the morning, in the afternoon - 18 days)
- Methotrexate 15 mg/m once a week. No. 2
- Hepatoprotector (heptor 400 mg 1 tablet 1 time per day-22 days)
- Folic acid 0.1 mg 2t 2 rd -6 days
- Desensitizing therapy (200 ml 0.9% Sodium Chloride-20 days)
- Local therapy (Comfoderm; Salicyl-dermatol ointment-22 days)
- Physiotherapeutic methods (Local PUVA-therapy-No. 13; UVB-311 nm-No. 13; External oxygen-ozone therapy-No. 11)

Dynamic Status

As the result of the treatment:

On the skin of the body there is a complete regression of rashes, with an outcome in residual hyperpigmentation. On the skin of the palms, a decrease in the brightness of rashes by 50%, regression of papular elements, elimination of peeling is observed (Fig. 2A).

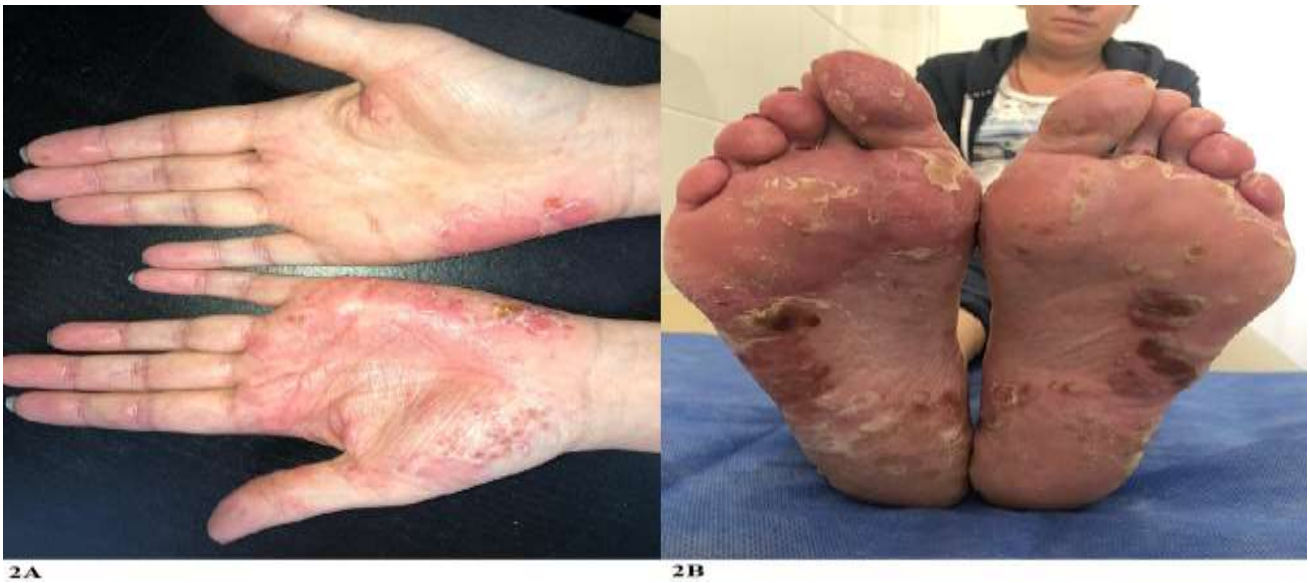

Figure 2: Regressive changes in the palms (2A) and feet (2B) as a result of the treatment

On the skin of the feet there is a decrease in the brightness of the rashes, the preservation of large-plate peeling (Fig. 2B)

Discussion

The presented clinical observation is an example of the development of an undesirable or paradoxical reaction in the form of progression of psoriatic skin lesions as a result of the pharmacological action of the preparation of the TNF-α inhibitor Certalizumab-pegol. Paradoxical adverse reactions (AR) are the occurrence of pathological conditions that are usually treated by the class of drugs with the use of which the reaction occurred, that is, the

suspected GEBA should initially have a proven therapeutic effect in the disease that it caused. True paradoxical AR includes psoriasis, Crohn's disease, and suppurative hydradenitis. During the development of GEBA, such reactions were not widespread and did not occur, but later on they began to be reported and a wide range of conditions associated with the use of GEBA was noted [12].

If we talk about the histological picture with pathological psoriasis, then it does not differ from true psoriasis. There are hypotheses explaining the occurrence of paradoxical AR during treatment with GEBA: an imbalance in the production of cytokines, a difference in the immunological properties of monoclonal antibodies and soluble TNF-α receptors.

Since psoriasis is a chronic disease, it requires long-term treatment. The choice of treatment is determined by the severity of the disease, concomitant conditions and the availability of medical care. Patients are usually divided into two groups - mild or moderate to severe psoriasis, depending on the clinical severity of the lesions, the percentage of the covered surface area of the body and the quality of life of the patient.

The clinical severity of the disease and the response to treatment can be graded, but the PASI scale is most commonly used. Mild or moderate psoriasis is treated with topical drugs using combinations of glucocorticoids, vitamin D analogues, and phototherapy. Moderate or severe psoriasis requires systemic treatment.

The traditional medicines used for systemic treatment of psoriasis are methotrexate, cyclosporin A and retinoids. Methotrexate is a structural analogue of folic acid that inhibits DNA synthesis by blocking the synthesis of thymidine and purine nucleotide biosynthesis. The initial recommended dose is 7.5-10 mg per week, but can be increased to 25 mg per week. A recent retrospective study revealed that the therapeutic effect was 33%, 47%, 64% at 3, 6, and 12 months, respectively (a decrease in the PASI scale from 50% to 70%) .

Despite studies showing the low efficacy of this drug and a wide range of known side effects, for example, its teratogenicity, it continues to be a long-term benefit for patients with first-line therapy if careful monitoring of liver function and analysis of blood cells is necessary. Cyclosporin A, mentioned above, is an immunosuppressive agent from the group of calcineurin inhibitors that inhibits T-cell activity. In this case, cyclosporine allows prolonging the period of remission and can be used as maintenance therapy up to 2 years .

The dose of the drug is 2.5-5 mg/kg body weight. Side effects of it are hypertension, nephrotoxicity, as well as non-melanoma skin cancer. In this regard, the drug is used as a periodic short-term therapy. Retinoids are natural or synthetic variants of vitamin A. Of this group, acitretin is most often used to treat psoriasis. It affects the processes of DNA transcription, acting through intracellular receptors, and thereby normalizes the proliferation and differentiation of keratinocytes.

The initial recommended dose of the drug is 0.3-0.5 mg/kg body weight per day, but can be increased to 1 mg/kg body weight per day. A multicenter, randomized trial revealed drug efficacy at 22.2% of PASI 75 patients and at 44.4% PASI 50 at 24 weeks. The main side effect associated with retinoids use is cheilitis, which can also be accompanied by conjunctivitis, alopecia, hepatitis and teratogenicity.

The above group of drugs has recently been supplemented with dimethyl fumarate and apremilast. Esters of fumaric acid, to which dimethyl fumarate belongs, are small molecules with immunomodulatory and anti-inflammatory properties. The exact mechanism of their action is unclear, but it is known to involve glutathione, which is able, among other things, to inhibit the transcriptional activity of NF-kB.

Dimethyl fumarate lowers the migratory capacity of slan + monocytes and also reduces the induction of T helper 1 and 17 responses [178j]. Side effects of the application are disorders of the gastrointestinal tract, hot flashes, as well as a decrease in the number of lymphocytes and leukocytes. Apremilast is an inhibitor of phosphodiesterase 4. When taken, it inhibits the hydrolysis of the secondary mediator of cAMP, which leads to a decrease in the expression of proinflammatory cytokines TNF, IFN and IL12 and an increase in the number of IL10.

The result is a pronounced anti-inflammatory

effect on keratinocytes, fibroblasts and endothelial cells. At 16 weeks of use, 33.1% of PASI patients were 75 [192-194j]. Side effects from the use of the drug are weak: disorders of the gastrointestinal tract (nausea, diarrhea) and upper respiratory tract (infection and nasopharyngitis).

The main advantage of its use is the absence of the need to monitor blood cells. In recent years, the treatment of psoriasis has become more focused on targeted biological drugs. They can be divided into 2 main groups: affecting the signaling pathway from TNFα and from IL23. The main drugs of the first group are TNF-α inhibitors etanercept, infliximab, adalimumab and sertolizumab. Etanercept is the only drug from this group that is not a monoclonal antibody, infliximab is a chimeric monoclonal IgG1 antibody, and adalimumab is a fully human monoclonal IgG1 antibody.

These substances neutralize the activity of TNF-α by binding to its soluble and membrane-bound forms and are used, in particular, for the treatment of psoriatic arthritis. They exhibit similar clinical efficacy: PASI 75 in 52% for etanercept, 59% for adalimumab, and 80% for infliximab.The stronger clinical effect of infliximab is most likely due to the fact that its chimeric nature gives a greater immunogenic potential, which can also increase the duration of the substance in the body.

Sertolizumab, unlike other drugs, is obtained by covalent PEGylation of a Fab fragment of an anti-TNF-α monoclonal antibody. This brings a number of biopharmaceutical improvements, including an increase in half-life and a decrease in immunogenicity. As a result, sertolizumab reaches a PASI score of 75 in 83%. Moreover, due to the absence of the Fc domain, it is not able to pass through the hematoplacental barrier; therefore it is approved for use during pregnancy and during breastfeeding.

Turning to the second group of biological drugs, we start with ustekinumab. Ustekinumab is a monoclonal antibody that binds the p40 subunit. Given that IL23 is a dimer consisting of p40 and p19 subunits, and that the p40 subunit is also present in IL12, which is involved in the differentiation of naive T cells into T helper cells 1, ustekinumab is also effective in psoriatic arthritis and Crohn's disease.

When used, PASI 75 is achieved in 61.2% of patients for a dosage of 45 mg and 72.4% for a dosage of 90 mg. When compared with anti-TNF drugs, it was found that it possesses much longer remains in the body. Among the side effects, nasopharyngitis, headaches are distinguished, but the most serious adverse event is obviously assumed to be high sensitivity to infections, including tuberculosis, by suppressing the maturation of T helper cells 1.

As a consequence, monoclonal antibodies have been developed directed against the second subunit of IL23 - p19. At present, guselkumab, tildrakizumab and risankizumab have been developed and are being studied. Their study revealed that at the 16th week of treatment, PASI 75 is achieved in 85.1%, 74%, 88%, PASI 90 in 73.3%, 52% and 81%, respectively. Moreover, a study of risankizumab revealed that a stable PASI value of 100 (up to 48 weeks) is achieved in a quarter of patients after 16 weeks of treatment.

Monoclonal antibodies directed to IL17 secreted by T helper 17 activated by IL23 have also been developed. These are IL17A blockers secukinumab and ixekizumab, as well as brodalumab type A IL17 receptor blocker. Secukinumab and ixekizumab demonstrate a rapid onset of therapeutic effect in the first week of treatment. By the 12th week of treatment, PASI 75 is achieved in 81.6% and 89.1%, and PASI 100 is achieved in 28.6% and 35.3%, respectively .

At the same time, drugs are approved for the treatment of psoriasis of the scalp and nails, which cannot be treated with traditional topical agents. Brodalumab, by inhibiting IL17 type A receptor, inhibits the biological activity of IL17A, IL17F, IL17A/F and IL17E (IL25). As a result of its use, by the 12th week of treatment, PASI 75 is achieved in 83.3%, and PASI 100 - 41.9%. The most dangerous probable side effect of its use is also a predisposition to infections. However, only candida infections of mild severity were recorded in the studies.

In addition, we list a few additional groups of drugs, most of which are still at the research stage:A3 adenosine receptor agonists capable of inhibiting NF-kB activation and inducing apoptosis of inflammatory cells.Janus kinase inhibitors that suppress signal transmission from a number of pro-inflammatory

cytokines, including interferons of types I and III and IL23. Finally, the only one of these drugs that has managed to get approval for use is apremilast. Phosphodiesterase inhibitor 4. The drug suppresses inflammation by reducing the production of TNF-α and IL23, as well as enhancing the production of anti-inflammatory molecules, for example, IL10.

Conclusion

The attitude to psoriasis, as a serious incurable disease, is gradually changing in the scientific medical environment. Modern clinical data of new treatment methods not only demonstrate optimistic results, but also contribute to a deeper understanding of the immunopathogenetic pathways of the development of this disease, identifying new potential targets for therapeutic intervention and diagnosis. And despite the fact that many studies are still being carried out or should be carried out, the hope of cure for this disease for millions of patients every year grows more and more. With the development of drug-induced psoriasis (de novo or exacerbation), topical corticosteroids (mainly: clobetasol, betamethasone) and drugs combined with corticosteroids (betamethasone in combination with calcipotriol) are considered the first line of therapy.

If therapy is ineffective or rashes reappear due to the use of TNF-α blockers, rashes are regarded as a class-specific effect, and the question of switching to a GIBT drug with a different mechanism of action is considered. In this case, the use of ustekinumab is most indicated. Class-mediated (paradoxical) AR - can be considered as a new group of AR, requiring a thorough study of the mechanisms of their development, as well as the registration of new, not yet described cases of AR that can occur during treatment with any representative of GEBA.

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