

DOI: 10.20514/2226-6704-2020-10-5-390-397

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Squamous Cell Skin Carcinoma in Systemic Lupus Erythematosus: Case Report and Literature Review

Abstract

The case report of squamous cell skin carcinoma diagnosed in a patient with systemic lupus erythematosus 26 years after the onset of rheumatic disease is presented. The features of this case included the absence of skin manifestations of systemic lupus erythematosus, the occurrence of a tumor at the site of ulcers and trophic disorders on the leg, a long period (6 years) from the onset of a ulcerative defect on the leg to the diagnosis of skin cancer (despite multiple biopsies and consultations of various specialists), as well as the occurrence of a cytokine release syndrome, which directly led to the death of the patient after the first use of the immune checkpoint inhibitors. Possible causes of skin cancer in patients with systemic lupus erythematosus, as well as the features of the cytokine release syndrome after immunotherapy for oncological diseases, are discussed.

Key words: *systemic lupus erythematosus, squamous cell carcinoma, skin, ulcers, cytokine release syndrome, immune checkpoint inhibitors*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Article received on 30.07.2020

Accepted for publication on 30.08.2020

For citation: Topolyanskaya S.V. Squamous Cell Skin Carcinoma in Systemic Lupus Erythematosus: Case Report and Literature Review. The Russian Archives of Internal Medicine. 2020; 10(5): 390-397. DOI: 10.20514/2226-6704-2020-10-5-390-397

SCC — squamous cell carcinoma of the skin, SLE — systemic lupus erythematosus

Introduction

Systemic lupus erythematosus (SLE) is one of the most common autoimmune rheumatic diseases. In cases of this disease, many organs and systems are involved in the pathological process. Its primary manifestations include damage to the kidneys, nervous system, cardiovascular system, skin, and mucous and serous membranes. SLE management

includes mandatory use of systemic glucocorticosteroids as monotherapy and in combination with other immunosuppressive agents. Despite a significant increase in the life expectancy of patients with SLE, the probability of death is still two to five times higher than for the general population. Mortality in SLE patients is caused by not only the manifestations and complications of the underlying disease but also other disorders, including cancer. Several

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cohort studies and meta-analyses were performed in the last decade. They sought to study the relationship between SLE and malignant neoplasms. However, their results were contradictory [1]. It has been convincingly demonstrated that patients with SLE are at significantly higher risk of oncohematological diseases (especially non-Hodgkin's lymphomas) and neoplasms of the reproductive system in women. As for skin cancer, data on this pathology are scarce and vary. For example, it was established that SLE does not increase but reduces the risk of melanoma.

In our observation, a 48-year-old woman was diagnosed with squamous cell carcinoma of the skin (SCC) in 26 years after the onset of systemic lupus erythematosus.

Case Report

A female patient I., 48, was for a long time observed at the Federal State Budgetary Research Institution "V. A. Nasonova Research Institute of Rheumatology" (Institute of Rheumatology) and the Department of Hospital Therapy No. 1 of the I. M. Sechenov First Moscow State Medical University with a diagnosis of systemic lupus erythematosus.

Anamnesis morbi: Onset of SLE at the age of 22, starting with the arthritis of the metatarsophalangeal joint. Later, migrating arthralgias appeared in almost all groups of joints and transient arthritis of small joints of hands; increased hair loss was reported. Fever, proteinuria, hematuria, edema of lower limbs, and dyspnea subsequently developed. The patient was admitted at the Institute of Rheumatology, where she was diagnosed with "systemic lupus erythematosus: glomerulonephritis, CNS damage, enanthema, leukopenia, immunological disorders", and treatment with oral glucocorticosteroids was started in combination with pulse therapy with methylprednisolone and cyclophosphamide; plasmapheresis sessions were occasionally performed. During the next 10 years, lupus nephritis was the main sign of SLE in this patient. Pulse therapy with glucocorticosteroids and cyclophosphamide was performed from time to time, as well as intramuscular injections of cyclophosphamide with frequent withdrawals due to poor tolerance. Considering the insufficient efficacy and poor tolerance to cyclophosphamide, this drug was discontinued, and other immunosuppressive agents were sequentially started – cyclosporin A and mycophenolate mofetil. The patient's

state remained stable; there were no other signs of SLE activity. Laboratory results showed persistent proteinuria (2–3 g/day) and high titers of antinuclear antibodies. The last exacerbation of SLE was 15 years ago when the patient had clinical manifestations of nephrotic syndrome, and the level of proteinuria increased to 7.42 g/day. Another course of pulse therapy with glucocorticosteroids and cyclophosphamide was performed, with a good effect. In subsequent years, the patient did not make regular follow-up visits; she took maintenance doses of methylprednisolone (8 mg/day) and occasionally azathioprine, in low doses. Proteinuria decreased to trace levels; there was occasionally no protein in urine; there were no changes in urinary sediment. Nitrogen-excreting renal function was relatively without changes, creatinine level increased to a maximum of 120 $\mu\text{mol/l}$, glomerular filtration rate corresponded to the 2–3a stage of chronic kidney disease. No other manifestations of SLE activity were observed. There was a slight increase in blood pressure, dizziness, "floaters" and double vision, and occasionally – short-term tunneling of vision. The patient also complained of increased development of ecchymoses, and with minor trauma, long-term non-healing wounds appeared on the anterior surface of lower legs. Hyperpigmentation and the slight induration of the skin of the anterior surface of lower legs progressed. Doppler ultrasound of the vessels of lower limbs revealed no significant changes in the arteries and veins of the lower limbs.

In August 2012, after a minor injury, a small ulcerous defect developed on the anterior surface of the upper third of the right lower leg. During the next two years, the size and depth of this ulcer increased. The patient was followed up by surgeons at her place of residence; local treatment was prescribed, with no effect. A histological test apparently revealed basal cell skin cancer cells but repeated biopsies (also at the P.A. Hertsen Moscow Oncology Research Institute (Hertsen MORI) showed no skin malignant neoplasms). The patient was examined several times at the Department of Dermatology and Dermatologic Oncology at the State Budgetary Healthcare Institution "M. F. Vladimirsky Moscow Regional Research and Clinical Institute" (MONIKI), the skin cancer diagnosis was rejected. Local treatment was continued, with no effect. Small ulcers appeared around the main ulcerous defect (Fig. 1), as well as a caseous discharge (Fig. 2).

The patient was re-examined at the Department of Wounds and Wound Infections of the A. V. Vishnevsky National Medical Research Center for Surgery. No data

indicating an active purulent process were obtained; further examination (exclusion of skin tuberculosis, deep mycoses, gangrenous pyoderma) was recommended. In the following months, a comprehensive examination was performed; the patient was examined several times by various specialists (from a vascular surgeon to a mycologist), including leading specialists in phthisiology, mycology and skin vasculites. The patient was many times hospitalized at the leading clinics in Moscow and St. Petersburg, but no exact diagnosis was made. Only local symptomatic treatment was carried out, without a significant effect. For several years, a biopsy of the skin flap and subcutaneous tissue was performed more than ten times; no data indicating cancer were obtained. Morphological changes were deemed non-specific and, possibly, the result of chronic inflammation: “Epidermis is moderately hyperplastic, with severe vacuole dystrophy



Figure 1. Ulcers on the anterior and lateral surface of the right leg

of cells of all layers. Derma with significant eosinophilia and homogenization (dermal hyalinosis). Vessels are dilated, single lymphocytes, plasma cells and histiocytes in the perivascular spaces.” In the past year, the patient was examined in the purulent surgery department. The edges of the ulcer were periodically excised and revised. Each surgical intervention was followed by a histological test; no data indicating a neoplasm were obtained. As a result of the surgical interventions, the size of ulcers decreased; there was no noticeable discharge (Fig. 3). However, during the next histological examination after excision of the ulcerous defect (07.2018), signs of a neoplasm were revealed: “At the level of the epidermis and dermis, abnormal squamous layers with high differentiation, with areas of hyperkeratosis, and foci of necrosis are determined.” Upon reviewing the histological examination results at the P. A. Hertsen Moscow Research Institute: “Areas of the skin with proliferation of highly differentiated SCC with infiltration of the dermis up to all edges of the site.” The diagnosis of verrucous squamous keratinizing cancer was made. Results of magnetic resonance imaging (MRI) of right lower leg (08.2018): “Skin of the anteroexternal surface of the upper third of right tibia is deformed in an area measuring 7 × 8 cm; tissue of solid structure is defined in its thickness, which forms an exophytic node 6.5 × 5.0 × 1.5 cm in size. On the inner surface of the distal biceps of the femur, a node measuring 1.0 × 1.5 × 1.0 cm was defined. A node 1.2 cm in diameter was also determined in subcutaneous fat of the anterior surface of the right lower leg.” In September 2018, at N. N. Blokhin National Medical Research Center of Oncology, a tumor was excised with reconstructive plastic surgery (Fig. 4).

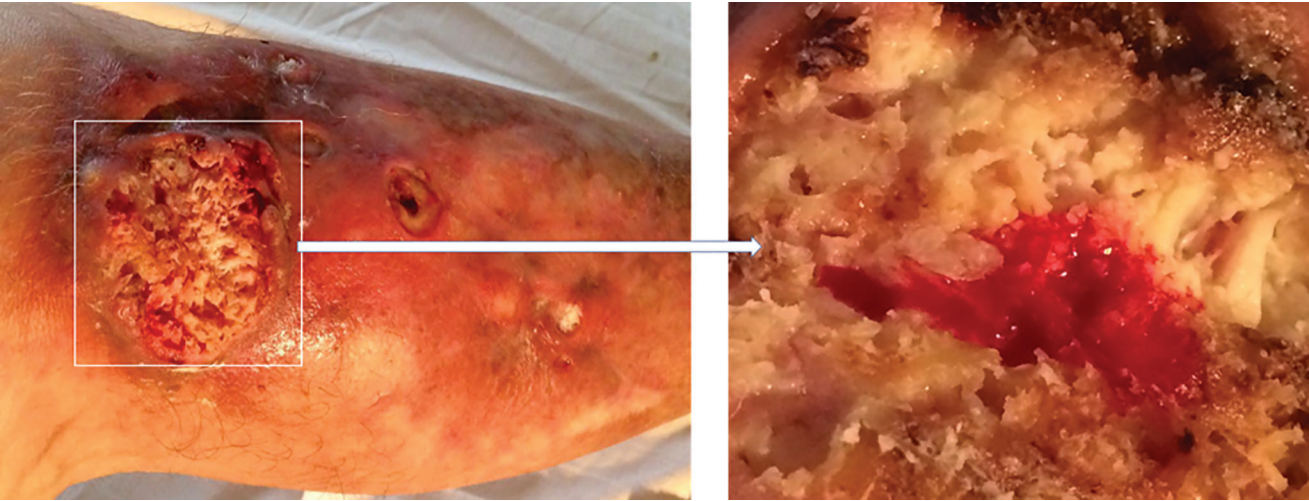


Figure 2. Leg ulcer with abnormal granulations and caseous-like discharge



Figure 3. Ulcers on the right leg after surgery and revision



Figure 4. Condition (1 month later) after excision of the tumor on the right leg

Results of intraoperative biopsy: "A tumor node is located in the skin in the form of growths of dense grayish-white tissue that degrades in an area measuring 7.5×6 cm; there is 2nd tumor node (4.5×3 cm) at a distance of 1 cm from it, and a second plaque-like mass (2.0×1.5 cm) at a distance of 5 cm from it. Micropreparations: tumor nodes have a structure of moderately differentiated keratinizing squamous cancer that grows into the subcutaneous fatty tissue and the underlying fibrous tissue."

Three months after tumor removal, metastases of malignant neoplasms to iliac lymph nodes on the right were found (Fig. 5). The patient was diagnosed with SCC T3N3M0.

Considering "borderline operability" and complex localization of the metastatic lesion of iliac lymph nodes, initial chemotherapy (paclitaxel in combination with carboplatin) was recommended. However, chemotherapy caused further progression of metastases; also, poor tolerability of this chemotherapy regimen was registered. Results of positron emission tomography combined with computed tomography (PET-CT) (04.2019, nine months after the diagnosis of SCC): "In the area of the right inguinal canal, a single conglomerate of external iliac and inguinal lymph nodes is found, up to $69 \times 52.5 \times 76$ mm in size, with necrotic changes in its central part and with hyperfixation of the radiopharmaceutical. Lymph nodes were also determined along external, internal and common iliac arteries, 8.5 mm in size. In soft tissues of the lower third of the right thigh, a pathological mass lesion, $49 \times 46 \times 52$ mm in size, was found, with necrotic changes and hyperfixation of the radiopharmaceutical, similar to the conglomerate in the iliac region.

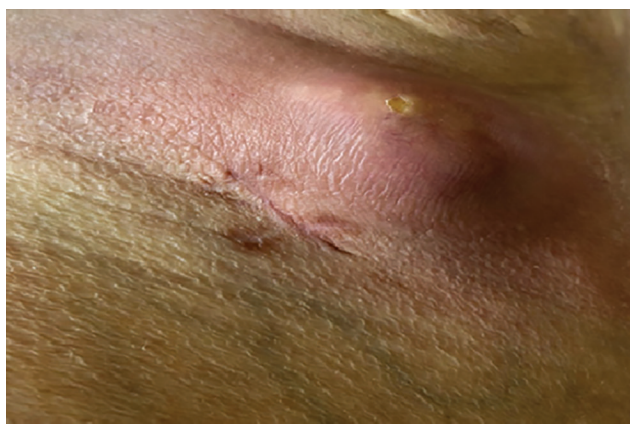


Figure 5. Right inguinal lymph node metastases (physical examination)

Conclusion: a picture of a pathological conglomerate of lymph nodes in the soft tissues of the lower third of the right thigh; a similar structure of a necrotic conglomerate of the right external iliac and inguinal lymph nodes, most likely of metastatic origin." An operation to remove inguinal lymph nodes was performed at the Federal State Budgetary Institution "Russian Research Center for X-ray Radiology" (RRCXR); necrotic changes in the conglomerate of lymph nodes were found, without distinct boundaries with surrounding tissues and dissemination. Following the operation, a second course of chemotherapy was carried out (carboplatin in combination with 5-fluorouracil), with no effect (disease progression). This type of tumor is refractory to both chemotherapy and radiation therapy, so no further chemotherapy attempts were undertaken.

In October 2019, an infusion of atezolizumab (anti-PD-L1 monoclonal antibodies) combined with dexamethasone was performed as a “last-resort treatment”. A day after administering atezolizumab, hectic fever (up to 40 degrees), chills, myalgia, a sharp decrease in blood pressure, and confusion were registered. Blood tests showed an increase in ESR up to 51 mm/h, WBC up to $16 \times 10^9/l$, a decrease in hemoglobin level to 100 g/l, an increase in C-reactive protein from 28.2 to 120.9 mg/l, an increase in creatinine (up to 11.6 mmol/l) and urea (up to 11.8 mmol/l), uric acid (up to 539 $\mu\text{mol/l}$), triglycerides (up to 3.2 mmol/l), potassium (up to 5.53 mmol/l), gamma-glutamyl transpeptidase (up to 120 U/l); urine tests revealed no pathology. Progressive multiple organ failure caused death.

Discussion

SCC is cancer originating from epidermal cells of the skin and/or hair follicles. This is the second most common neoplasm (after basal cell carcinoma) in the group of non-melanoma skin tumors [2]. Risk factors for SCC include old age, exposure to ultraviolet radiation, a certain (light) skin phototype, and immune deficiency states [2]. One characteristic of SCC is that this tumor is the most common neoplasm that develops at the site of a long-existing scar or a long-term non-healing wound; this form of SCC has a worse prognosis and often recurs after treatment [2].

According to Hertsen MORI, the average age of patients diagnosed with this skin cancer is 70.5 years; stage III of this disease is registered at the first visit only in 1.6% of patients, and stage IV — in 0.5% of patients. The average age of people dying from this neoplasm is 77.6 years; mortality in the first year of disease is 10.6% [2]. In contrast to the general population, our patient was diagnosed with SCC at the age of 48, stage III was established almost immediately, and she died 16 months after the tumor was detected.

In our observation, factors that can trigger the onset and progression of skin cancer include long-term immunosuppression with various immunosuppressants, an autoimmune disease with pathological features of the immune system, a long-term non-healing (more than six years) ulcerous defect on the anterior surface of the lower leg, and, before that, multiple recurrent wounds of the lower legs

after minimal trauma. Light skin phototype can be considered an additional factor. It should be noted, however, that due to the long-term history of SLE, the patient avoided excessive exposure to ultraviolet radiation. Therefore, the role of this factor can be excluded. Moreover, the neoplasm developed in the upper third of the lower leg, i.e., in an area that was constantly covered with clothing (trousers).

One of the key features of the described clinical case was a long (over 26 years) history of systemic lupus erythematosus. According to the literature, skin cancer is a rare but severe complication of SLE [3]. The immune system abnormality typical for SLE and its regulation disorders can prevent the removal of tumor cells and, ultimately, contribute to an increase in the risk of neoplasms [1, 3]. Persistent inflammation in patients with lupus-induced skin lesion is considered to be another potential risk factor for skin cancer [3]. This variant of skin syndrome is characterized by the accumulation of T-regulatory lymphocytes, mast cells, macrophages, and a significant increase in the level of the transforming growth factor $\beta 1$ and interleukin-6 that stimulate carcinogenesis. Pro-oncogenic immune cells and cytokines in patients with lupus are considered capable of overcoming the tumor-suppressing effects of Th1 lymphocytes and stimulating the development of skin cancer [3].

It should be emphasized that our patient had no reported manifestations of skin syndrome due to SLE throughout the course of the disease. At the same time, available literature sources usually describe cases or series of cases of skin cancer in patients who already have lupus erythematosus in the form of discoid or subacute cutaneous lupus erythematosus. According to some authors, SCC that occurs in patients with discoid lupus erythematosus has a more aggressive course with an increased frequency of relapses, metastasis and mortality compared to other forms of skin cancer [4].

The interval between the onset of lupus and SCC usually varies from 4 to 20 years [4]. The following are factors that increase the risk of SCC with underlying lupus: age over 40 years, male gender, exposure to ultraviolet radiation, skin pigmentation, and chronic inflammatory processes [4]. In our observation, the 48-year-old female patient was diagnosed with skin cancer 26 years after the onset of SLE. In this case, significant hyperpigmentation

of the skin of the lower legs, especially on their anterior surface, and long-term non-healing ulcers on the lower legs were registered.

Our observation confirms literature data on the unfavorable prognosis of SCC that developed at the site of the scar or long-term non-healing ulcer. According to French researchers who studied the transformation of ulcers of the lower limbs in 80 patients of senile age, ulcerous defects usually precede the onset of skin cancer much earlier (at least 3 years) (as in the case of our patient) [5]. Almost all patients in this study had SCC. Findings that were unusual for “vascular” ulcers included pathological granulation, abnormal vegetations, non-healing, and unusual localization of ulcers; our patient had all these signs. One in three patients in this group died (because of metastases); late diagnosis of neoplasm was the main cause of death. More than half of the patients (57%) underwent amputation of the lower limbs [5]. However, our patient categorically refused this intervention. Immunosuppressive agents used to treat SLE (cyclosporin A, mycophenolate mofetil, tacrolimus, and azathioprine) can also contribute to SCC by suppressing antitumor immune response in the skin [3]. As mentioned earlier, due to the refractory course of lupus nephritis, our patient received cyclosporine A, mycophenolate mofetil, azathioprine, and cyclophosphamide. However, over the last 15 years, she took only maintenance doses of glucocorticosteroids and, occasionally, azathioprine. Rapid death a few days after the administration of atesolizumab can be considered another specific feature of our patient. Atesolizumab is a monoclonal antibody (IgG4) that directly binds to PD-L1 and belongs to the group of modern antitumor drugs referred to as immune checkpoint inhibitors (checkpoint inhibitors). The mechanism of action of these drugs is aimed at restoring normal antitumor immune response by blocking inhibitory receptors of T-lymphocytes, the so-called key points of immunity (in particular, programmed cell death protein (PD-1) and its ligands PD-L1 and PD-L2), allowing tumor cells “evade” immune surveillance. Blocking the signaling pathway of the checkpoints of the PD-1/PD-L1 immune response enhances antitumor immune response, restores the activity of cytotoxic T-lymphocytes, and reduces the number and activity of T-suppressors.

The effectiveness of immune checkpoint inhibitors in managing different oncological diseases has been demonstrated in recent years. However, due to the inhibition of several parts of the immune system, drugs of this type enhance not only immune activity against cancer cells but also against unchanged cells of different organs and systems, leading to a number of immune-mediated adverse reactions. The most severe side effect is cytokine release syndrome — a systemic inflammatory disease characterized by a massive release of cytokines [6]. Cytokine release syndrome can manifest in various symptoms, from moderate to life-threatening and sometimes fatal. Mild manifestations of cytokine release syndrome include fever, general weakness and malaise, nausea, vomiting, headache, rash, arthralgia and myalgia. More severe cases are characterized by very high fever, arterial hypotension requiring high doses of vasopressor drugs, and can lead to uncontrolled systemic inflammatory reaction with shock, disseminated intravascular coagulation syndrome, and multiple organ failure [6–7]. In cases of cytokine release syndrome, different laboratory abnormalities are often found, particularly cytopenia, coagulopathy, increased levels of liver enzymes and creatinine, and a high C-reactive protein level [6–7]. The term “cytokine release syndrome” was first proposed in the early 1990s with the use of anti-T-cell antibodies as an immunosuppressive agent. Subsequently, this syndrome was described after using various monoclonal antibodies (e.g., rituximab), some chemotherapeutic agents and immunotherapy drugs, including immune checkpoint inhibitors [7]. A cytokine “storm” caused by the massive stimulation of T-lymphocytes can also develop in severe viral infections, including novel coronavirus infection and influenza [8–9].

The pathogenesis of cytokine release syndrome is based primarily on the activation of T-lymphocytes, which leads to increased release of gamma-interferon and tumor necrosis factor-alpha. This results in the activation of macrophages, dendritic cells, other immune and endothelial cells that additionally release pro-inflammatory cytokines. It is crucial that macrophages and endothelial cells produce a large amount of interleukin-6 that activates T-lymphocytes and other

immune cells via a positive feedback mechanism, which, in turn, leads to a cytokine “storm” [7]. The largest series of cases of cytokine release syndrome during treatment with checkpoint inhibitors (including atesolizumab) included 58 patients; the results were published in May 2020 [6]. In this group, cytokine release syndrome developed 1–18 weeks after starting treatment with immune checkpoint inhibitors and led to death in only two cases. According to the authors of this article, the following are the most common clinical manifestations of cytokine release syndrome: constitutional symptoms (general weakness, fatigue, asthenia, fever (most often), arthralgia, myalgia; skin rash; pathology of the gastrointestinal tract (nausea, diarrhea); respiratory damage (pulmonary edema, acute respiratory distress syndrome, respiratory failure, pleural effusion, hypoxia); cardiovascular pathology (tachycardia, arterial hypotension); nephropathy (acute kidney damage, nephritis); neurological symptoms (headaches, tremor) [6]. In the patient we described, the signs of cytokine release syndrome included hectic fever with chills,

severe arterial hypotension requiring the use of vasopressor drugs, tachycardia uncontrolled with standard beta-blockers, damage to the central nervous system, a significant increase in C-reactive protein level, as well as other manifestations (Fig. 6). Our observation does not include cytopenia, unlike other descriptions of cytokine release syndrome or cytokine storm. However, in the above-mentioned group of patients who received immune checkpoint inhibitors, cytopenia was also extremely rare — one case of anemia, leukopenia, and lymphopenia, two cases of thrombocytopenia, and two cases of neutropenia [6]. Management of patients with cytokine release syndrome depends on the severity of this pathological condition. High fever and a significantly increased C-reactive protein level were proposed as routine prognostic markers of this syndrome (especially if the level of interleukin-6, subpopulations of T-lymphocytes and other immune cells cannot be determined) [7]. In cases of mild manifestations of cytokine release syndrome, only symptomatic therapy is used (in particular, antihistamines

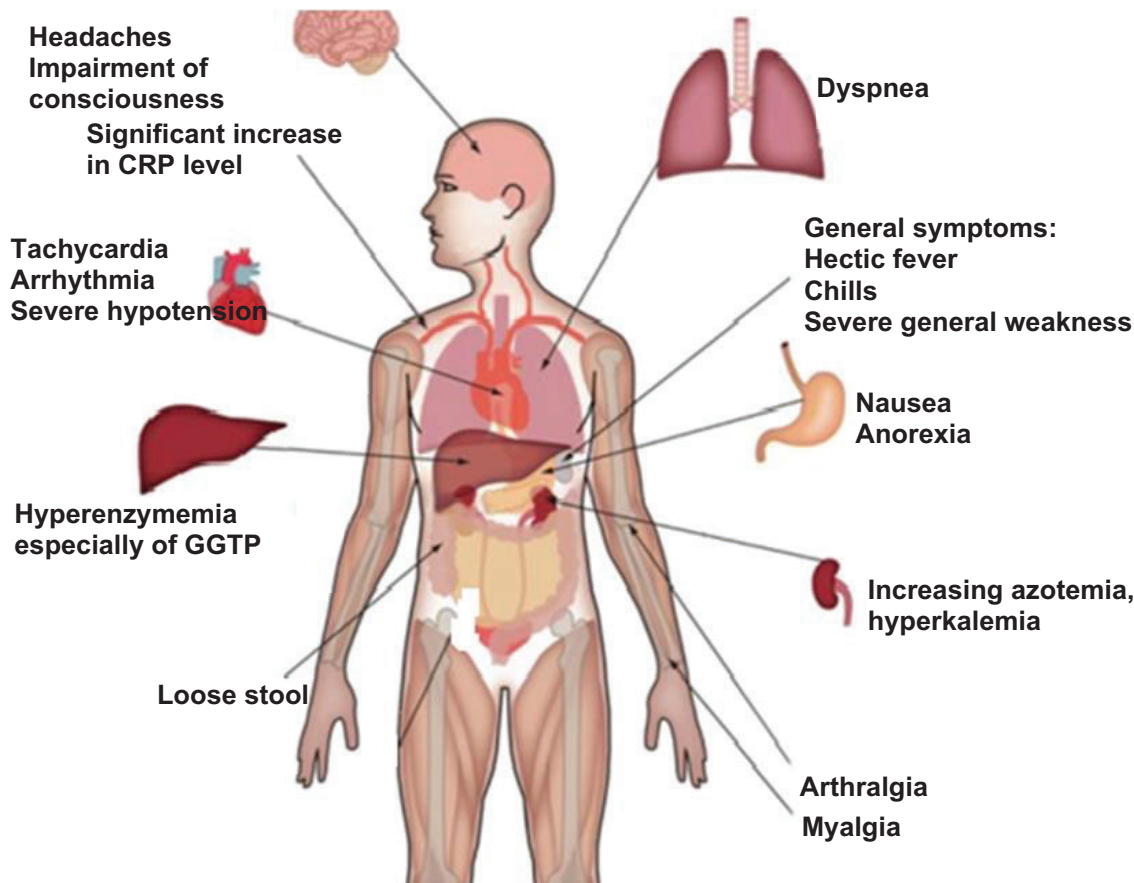


Figure 6. Clinical manifestations of cytokine release syndrome in the described patient

and antipyretic drugs) [7]. Patients with a severe course of this syndrome are recommended to immediately take anti-interleukin-6 monoclonal antibodies (for example, tocilizumab). Glucocorticosteroids should not be prescribed as first-line drugs in such cases; they should be used in patients with ineffective anti-interleukin-6 monoclonal antibodies and in cases of severe CNS injury. If anti-interleukin-6 antibodies and glucocorticosteroids are ineffective, treatment can be carried out with monoclonal antibodies against tumor necrosis factor- α or interleukin-1 or using immunosorption [7]. Unfortunately, our patient was not able to use these methods of treating severe cytokine release syndrome (except glucocorticosteroids); she died because of increasing multiple organ failure.

Therefore, the main features of the described clinical case are:

1. The development of SCC 26 years after the onset of systemic lupus erythematosus in a patient who never had any skin manifestations of SLE.
2. The presence of such a risk factor for SCC as immunosuppression (associated with SLE and with prolonged use of immunosuppressive agents).
3. The development of SCC at the site of a long-term non-healing (for 6 years) ulcerous defect on the anterior surface of the upper third of the right lower leg.
4. An unclear (to this day) etiology of an ulcer of the lower leg despite numerous consultations at leading clinical centers in Russia and many histological tests of the skin and subcutaneous tissue. The ulcer was characterized by a specific localization (the upper third of the anterior surface of the lower leg), pathological granulation and abnormal vegetations, and failure to heal for many years despite the ongoing treatment.
5. Rapid progression of SCC with the development of metastases, despite ongoing surgical and chemotherapeutic treatment, in contrast to the sporadic forms of this tumor that responds well to resection.
6. The development of probable cytokine release syndrome after the first administration of an immune checkpoint inhibitor in a patient with an autoimmune disease (SLE).

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