CLINICAL CASE

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CLINICAL CASE OF THE DEVELOPMENT OF SWEET'S SYNDROME IN A PATIENT WITH MYELODYSPLASTIC SYNDROME

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Sweet's syndrome is a rare type of dermatoses, which characterized by a recurrent course, painful bright red papules, inflammatory plaques, fever and neutrophilic leukocytosis. The article demonstrates a clinical case of Sweet's syndrome associated with hypomethylating agents in patient with myelodysplastic syndrome. The diagnosis was verified based on clinical features which included purplish-red colored skin plaques with ulcerative-necrotic defects right after azacitidine and decitabine therapy; profound therapeutic effect from steroids, plasmapheresis, ineffectiveness of antibiotics, antifungal drugs; increasing the level of neutrophils. The concurrent severe course of the diseases was complicated by extensive necrotic skin lesions of the lower extremities, which required surgical intervention. The recurrent course of Sweet's syndrome and the ineffectiveness of maintenance doses of prednisolone required a consideration of changing treatment approach of myelodysplastic syndrome with the discontinuation of hypomethylating agents.

Therapeutic tactics for patients with a rare disease, Sweet's syndrome, should be selected individually, taking into account the form of the disease and concomitant pathology.

Keywords: Myelodysplastic syndrome, skin vasculitis, Sweet's syndrome, acute neutrophilic dermatosis.

Introduction. Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal blood disorders characterized by cytopenia, signs of dysmyelopoiesis and a high risk of transformation into acute myeloid leukemia. Clinical manifestations of MDS are nonspecific and are most often caused by quantitative and qualitative changes in complete blood count (cytopenic syndrome, infectious complications). In 10% of cases, MDS starts with autoimmune and inflammatory manifestations, among which the most common are anemia, thrombocytopenia, and less often polyserositis, arthritis and skin vasculitis [2]. At the same time, the results of previous studies have proven a significantly higher risk of developing MDS and acute myeloid leukemia in people with autoimmune diseases [6].

Montoro J. et al. showed that autoimmune disorders, detected in 48% of patients with MDS, significantly worsen overall survival (69% compared with 88% in patients without autoimmune diseases), and also increase the incidence of infectious complications and mortality rates (71,0% compared with 47,2%, p = 0,0056) [3, 4].

In some patients with MDS, the autoimmune process manifests with vasculitis, the prevalence of which varies from 5 to 60% according to data of different investigators [3, 13]. At the same time, small vessels involvement (leukocytoclastic vasculitis) is most often observed, which is a serious clinical problem that complicates the verification of diagnosis and treatment of MDS. Histologically, this type of vasculitis is characterized by inflammation of small vessels, in which the inflammatory infiltrate is represented by neutrophils. One of the rare forms of cutaneous vasculitis associated with neutrophilia is Sweet's syndrome, characterized by a relapsing course, painful bright red papules and inflammatory plaques, fever and neutrophilic leukocytosis [8].

According to data of literature, the development of Sweet's syndrome is described in 10% of patients with MDS and acute myeloid leukemia. A potential trigger for the development of dermatosis can be both the disease itself and the ongoing anticancer therapy. To date, a number of clinical observations have been published proving the relationship between the onset of Sweet's syndrome and the hypomethylating agent 5-azacytidine [5, 10, 11, 14]. The results of these works have demonstrated the effectiveness of immunosuppressive therapy in relieving the clinical feature of neutrophilic dermatosis, however, long-term use of glucocorticosteroids in patients with hematologic malignancies is associated with an increased risk of infections, which explains the relevance of this problem [10].

The aim of the study: to describe a clinical case of Sweet's syndrome that developed during therapy with hypomethylating agents in patient with myelodysplastic syndrome.

Clinical case. Patient N., 51 years old, first contacted a hematologist in July 2022 with complaints of anemic syndrome – weakness, dizziness, fatigue, shortness of breath on exertion. During examination complete blood count revealed cytopenia of three blood lineages (erythrocytes 2.48 x 10^{12}/l, hemoglobin 82 g/l, leukocytes 2,02 x 10^{9}/l, platelets 104x10^{9}/l). Bone marrow examination demonstrated hypercellular smear with an increase in the number of blast cells up to 11,5%, as well as signs of dysgranulo-, erythro-, and megakaryocytopoiesis characteristic of MDS. An immunophenotypic study revealed myeloid lineage of blast cells (6%) with expression of CD13, CD33, CD177+, lines of nonspecific markers HLD-DR4+, CD38+, CD34+. Based on the results of trephine biopsy of the bone marrow, a histological signs of hypercellular bone marrow with secondary hyperplasia and dysplasia of granulocytopoiesis; MDS with excess blasts 2 was revealed. Thus, the diagnosis was verified as MDS refractory anemia with excess blasts - 2, a high-risk group according to IPSS (5,5).

According to the Federal clinical guide-

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lines for the treatment of patients with MDS, from 09.06.2022 to 10.06.2022, the first course of chemotherapy with low doses of cytarabine was carried out. There were no complications after treatment; bone marrow biopsy showed a reduction of blast cells to 4,6%.

Next, treatment protocol was changed to hypomethylating agent 5-azacytidine 75 mg/2 days 1–7. The first cycle with standard doses was carried out from 2.11.2022 to 8.11.2022 and was complicated by prolonged myelotoxic agranulocytosis with infectious complications, febrile fever, as well as the development of extensive ulcerative-necrotic lesions of the skin of the lower extremities. Thus, on the 1st of December 2022, at the 23rd day of azacitidine therapy completion, the appearance of an area of painful skin thickening on the right leg, accompanied by an increase in the level of neutrophils, was noted (Fig. 1.1, Fig. 2). According to ultrasound examination, local thickening of tissue up to 1.9 cm was noted in the lower third leg along the inner surface. Taking into account the presence of febrile fever in the post-cytostatic period, antibacterial and antifungal therapy was prescribed. In dynamics, there was an increase of area of skin lesions in lower extremities with necrosis of the skin and adjacent tissues, progressive pain that is not relieved by taking non-steroidal anti-inflammatory drugs. Since 5th of December 2022, worsening of pain in the right leg and expansion of involved tissue have been noted. A differential diagnosis was carried out between erysipelas, mucormycosis, thrombophlebitis of the veins of the lower extremity, taking into account data from instrumental studies indicating infiltration of soft tissues, echo signs of moderate phlebitis of the main trunk of the great saphenous vein at the level of the right lower third leg. Repeated microbiological examinations of the affected skin area did not reveal pathological growth. According to the results of histological examination, necrotic masses were obtained twice, which did not allow verification of the diagnosis. Local therapy was carried out in volume - heparin ointment, compression bandaging of the lower extremities and venotonic therapy.

On December 13, 2022 with prolonged febrile fever, progressive necrotic lesions of the right lower limb (Fig. 1.2), patient was admitted to the intensive care unit (ICU) of the surgical hospital, where for the first time diagnosis of cutaneous vasculitis in the stage of incomplete drug remission was verified. Taking into account the lack of effect from massive antibacterial and antifungal therapy, we suspected the immunoinflammatory nature of the skin changes. In this regard, pulse therapy with methylprednisolone and discrete plasmapheresis sessions were initiated, achieving a rapid clinical response with normalization of temperature. Surgical debridement with necrectomy was performed within the involved area of skin (Fig. 1.3).

Taking into account the development of life-threatening complications, it was decided to abstain from chemotherapy, but in March 2023, progression of the underlying disease was registered with an increase of blast cells in bone marrow up to 7,4% and increased need for blood transfusions, which was an indication for the resumption of specific therapy. The 2nd course of 5-azacytidine therapy was complicated by the appearance of similar pustular skin lesioms in the inguinal area and in the middle third of the right forearm with febrile fever, which regressed after the administration of prednisolone at a dose of 90 mg/day. Subsequently, 2 more courses of therapy with 5-azacytidine were carried out with low doses of prednisolone 15–30 mg/day. Considering the recurrent course of dermatosis with acute fever, neutrophilia (Fig. 2), the therapeutic effect of immunosuppressive therapy with prednisolone, Sweet's syndrome, or acute febrile neutrophilic dermatosis, was suspected in this case. This diagnosis was confirmed based on anamnesis of the disease (the appearance of rashes after a course of chemotherapy, a profound therapeutic effect from glucocorticosteroids, plasmapheresis, lack of effect from treatment with antibiotics, antifungal drugs); clinical presentation (presence of merging plaques of purplish-red color, forming ulcerative-necrotic defects); laboratory findings (increase of neutrophil levels at same time with the appearance of plaques, progressive anemia and thrombocytopenia in a complete blood count).

Since July 2023, taking into account recurrent ulcerative necrotic skin lesions associated with the administration of azacitidine, therapy was changed to decitabine 20 mg/m2 for days 1–5. However, the post-course period was also complicated by prolonged febrile fever, the appearance of ulcerative formations on the dorsum of both hands with severe pain, requiring opioid analgesics. Pathogenetic therapy with prednisolone 90 mg/day, combined antimicrobial therapy, and discrete plasmapheresis sessions were performed with improvement. Despite the relief of the life-threatening condition, it was decided to refrain from specific therapy in the future. Blood transfusion and symptomatic therapy are recommended. Currently, the patient's condition is satisfactory, and dynamic observation continues.

Discussion. The presented clinical case demonstrates the complexity of management of patients with a competing course of a rare disease, Sweet's syndrome, and MDS. Firstly, treatment of hemoblastosis requires strict adherence to the doses and intervals of administration of chemotherapy drugs. The development of life-threatening complications,

Fig 1.1 Fig 1.2 Fig 1.3

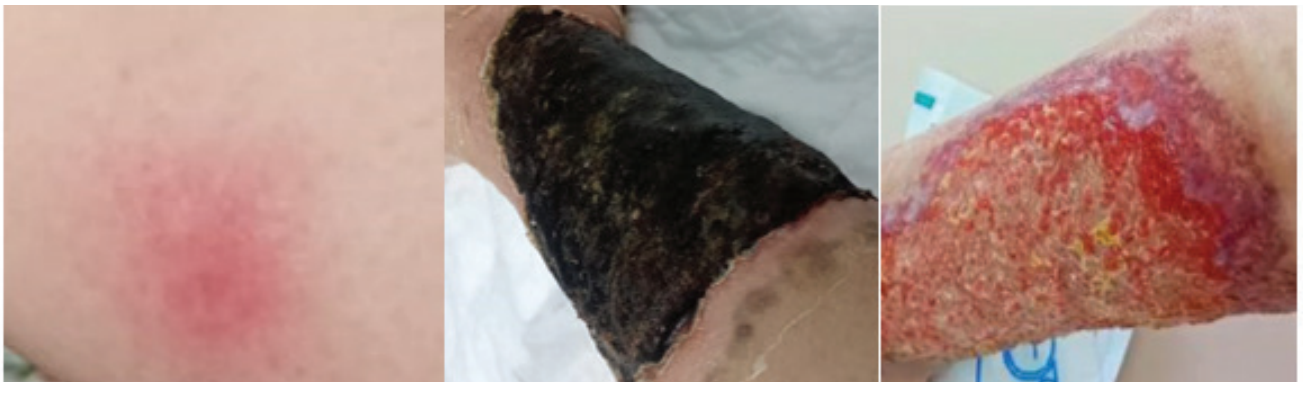

Fig. 1. Dynamics of skin lesions in patient (december 2022 – february 2023)

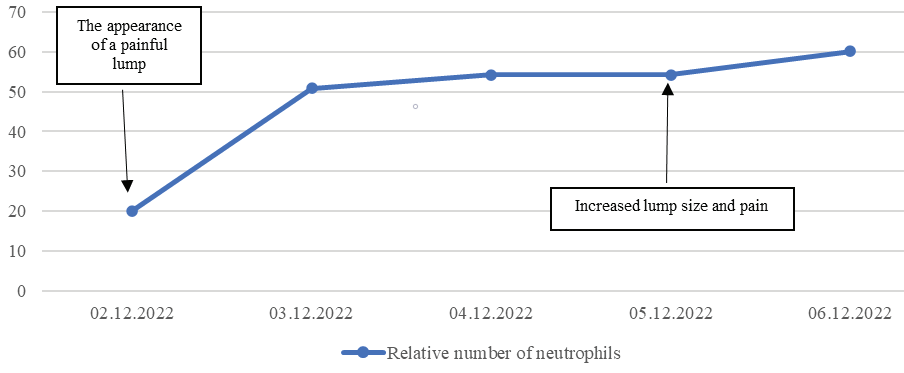

Fig. 2. Dynamics of neutrophils level

Diagnostic criteria of classic form of Sweet's syndrome

	Major criteria	Minor criteria
Diagnostic criteria	Sudden appearance of painful, erythematous skin nodules or plaques.	Fever 380C or more
		Association with hematologic or visceral malignancy, inflammatory disease or pregnancy, or previous upper respiratory tract infection
	Histological signs of a dense neutrophilic infiltrate without signs of leukocytoclastic vasculitis	Pronounced response to treatment with corticosteroids
		Abnormal laboratory tests (3 of 4): ESR > 20 mm/h, high CRP, leukocytes > 8000, neutrophils > 70%

which required intensive care unit administration, led to discontinuations of courses, which may worsen a prognosis of the disease in patient with high-risk group. Secondly, accurate verification of diagnosis in this cohort of patients is often difficult due to the atypical course of the disease caused by secondary immunodeficiency and persistent thrombocytopenia, that limits surgical interventions and biopsy of the affected area.

In this patient, the undulating course of dermatosis, clearly associated with chemotherapy and characterized by the appearance of painful erythematous pseudovesicular plaques, fever and neutrophilia, allowed us to make a diagnosis of Sweet's syndrome, which is an inflammatory dermatoses. The prevalence of the disease is 1–9 cases per 1 million population. In the Russian Federation, single clinical cases are described [1]. According to the literature, the disease is more commonly seen in women aged 30 to 60 years. Depending on the cause of the development of this syndrome, three clinical forms are distinguished: classic, cancer- and drug-related. Taking into account the manifestation of acute febrile neutrophilic dermatosis after courses of hypomethylating drugs (5-azacytidine and decitabine), the described case most likely corresponds to the drug-related form. It is described that most commonly drug-related form is associated with the administration of granulocyte colony-stimulating factor (G-CSF), which also occurred in this clinical case. In addition, some immunosuppressive agents, such as azathioprine, have also been described as triggers for the development of Sweet's syndrome, which is based on a type IV hypersensitivity reaction that manifests within 1–4 weeks of taking an immunosuppressive drug [8,9].

The most likely theory of pathogenesis explaining the connection of Sweet's syndrome with malignant neoplasms is the overproduction of pro-inflammatory cytokines and growth factors (G-CSF and GM-CSF). Excessive production of G-CSF stimulates the proliferation of granulocyte lineage cells, which leads to an increase in the level of neutrophils [8]. In case of initial neutropenia caused by hematopoietic depression, the differential diagnosis of this condition can be difficult. However, figure 2 shows an increase in the level of neutrophils by 3 times, accompanied by the appearance of characteristic skin elements and fever. It should be noted that, according to the literature, leukocytosis is not always observed. Especially in patients with Sweet's syndrome of paraneoplastic origin, anemia, thrombocytopenia, and neutropenia may instead be observed [8].

5-azacytidine is characterized by immunoregulatory properties, which are due to its ability to suppress the secretion of proinflammatory cytokines and increase the number of CD4+CD25+/forkhead-box-p3+ T-regulatory cells. Previous clinical case described that the anti-inflammatory properties of 5-azacytidine make it possible in some cases to relieve neutrophilic dermatosis, however, in some cases, the development of Sweet's syndrome in patients with MDS may be considered as an adverse effect of 5-azacytidine therapy [5, 7, 10].

Dermatological manifestations of Sweet's syndrome were characterized by appearance at the site of skin damages: microtraumas, including drug injection sites, biopsies, radiation therapy areas, insect bites [1, 5]. Thus, one of the episodes of the appearance of skin plaques in this clinical case was mediated by multiple attempts at venipuncture.

The diagnosis of Sweet's syndrome is verified based on diagnostic criteria proposed by S. Su and C. Liu in 1986, later modified in 1994 by P. van den Driesch (Table) [12]. In this clinical case, the patient had 1 major and 4 minor criteria, and a biopsy of skin elements was not performed due to the high risk of progression of ulcerative-necrotic lesions and the development of hemorrhagic complications in the presence of critical thrombocytopenia. In our opinion, the available data were sufficient to verify this rare clinical condition and change the patient's management tactics.

Conclusion: Description of clinical case of rare diseases is necessary to increase the awareness of doctors of various specialties and expand the range of differential diagnosis of pathological conditions with a similar clinical feature. Therapeutic tactics for patients with a rare disease, Sweet's syndrome, should be selected individually, taking into account the form of the disease, concomitant and competing pathology.

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