

КЛИНИЧЕСКИЙ СЛУЧАЙ CASE REPORT

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CUTANEOUS MANIFESTATIONS OF ANCA-ASSOCIATED VASCULITIS AND IMMUNOSUPPRESSIVE THERAPY: CAUSE-EFFECT RELATIONSHIPS (A CASE REPORT)

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◆ Granulomatosis with polyangiitis, formerly known as Wegener's granulomatosis, is an autoimmune ANCA-associated systemic vasculitis characterized by extensive damage to multiple organs and systems. Besides a typical clinical triad of ENT, lungs, and kidneys injury, various types of skin lesions can be found in 10–50% of cases. A severe course of the disease and low survival of patients often requires using aggressive treatment in a form of combined immunosuppressive therapy. On the one hand, it generally improves the prognosis, and on the other is itself associated with numerous complications. One of them is a secondary infection. Skin is the second most common localization of infection after the respiratory system. Preceding skin lesions caused by vasculitis may increase the risk of infection. Thus, patients with ANCA-associated vasculitis should be carefully observed for cutaneous manifestation, both before and during the immunosuppressive therapy.

◆ **Keywords:** granulomatosis with polyangiitis; ANCA; vasculitis; infection; treatment; complication; glucocorticoids.

КОЖНЫЕ ПРОЯВЛЕНИЯ АНЦА-АССОЦИИРОВАННЫХ ВАСКУЛИТОВ И ИММУНОСУПРЕССИВНАЯ ТЕРАПИЯ: ПРИЧИННО-СЛЕДСТВЕННЫЕ СВЯЗИ (ОПИСАНИЕ КЛИНИЧЕСКОГО СЛУЧАЯ)

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◆ Гранулематоз с полиангиитом, ранее именовавшийся гранулематозом Вегенера, — аутоиммунное заболевание из группы АНЦА-ассоциированных системных васкулитов, для которых характерно обширное поражение различных органов и систем. Помимо вовлечения ЛОР-органов, легких и почек — типичной клинической триады — в 10–50 % случаев можно обнаружить разнообразные варианты поражения кожи. В связи с тяжелым течением заболевания и низкой выживаемостью пациентов зачастую необходимо назначение агрессивного лечения в виде комбинированной иммуносупрессивной терапии. Это, с одной стороны, в целом улучшает прогноз, но с другой — вызывает всевозможные осложнения. Одним из таких осложнений является присоединение вторичной инфекции. На втором месте по частоте встречаемости после поражения дыхательной системы встречаются поражения кожи. Предшествующие кожные повреждения в рамках

васкулита могут увеличивать вероятность инфицирования. Таким образом, пациентов с АНЦА-ассоциированными васкулитами необходимо тщательно наблюдать с целью обнаружения кожных проявлений как до начала, так во время проведения иммуносупрессивной терапии.

♦ **Ключевые слова:** гранулематоз с полиангиитом; АНЦА; васкулит; инфекция; лечение; осложнение; глюкокортикоиды.

Granulomatosis with polyangiitis (GPA) is a granulomatous inflammation of the respiratory tract and necrotizing vasculitis, affecting mainly small and medium-sized vessels (capillaries, venules, arterioles, arteries, and veins), usually combined with necrotizing glomerulonephritis [1]. According to the 2012 Chapel-Hill classification, GPA refers to systemic vasculitis associated with the production of antineutrophil cytoplasmic antibodies (ANCA) [2].

Its total incidence worldwide is 2–12 per 1 million people, and its prevalence is 23–160 per 1 million people, affecting men and women equally. At the same time, GPA onset can be at any age, but the highest peak incidence is from 45 to 60 years of age [3]. The work presents data on a possible genetic predisposition to the development of GPA associated with the inheritance of alleles encoding alpha-1-antitrypsin (*SERPINA1*) and proteinase-3 (*PRTN3*) [4].

Like other systemic vasculitis, GPA is characterized by an extensive lesion of organs and systems. The combination of lesions of the ENT organs, lungs, and kidneys is of key significance in the clinical presentation, which, together with the histological signs of granulomatous inflammation, constitutes the classification criteria for GPA of the 1990 American College of Rheumatology (ACR) [5]. In addition, the clinical presentation with this type of vasculitis can often reveal subglottic stenosis of the larynx, neuropathy, pseudotumor of the orbit, hearing impairment, and various types of skin lesions [6]. According to various estimates, the latter are noted in 10%–50% of cases, often serving as the first manifestation of ANCA-associated vasculitis (ANCA-AV), which develops into a clinically significant damage to the vital organs [3]. Skin lesions in GPA are often found on the lower extremities and on the face and scalp. Most often, lesions are presented as mildly elevated hemorrhagic eruption (type of palpable purpura) and, less often, as urticarial rash, painful erythematous nodules, or ulcerative-necrotic abnormalities. These eruptive elements in GPA are often accompanied by livedo reticularis, which is an ischemic

dermopathy characterized by symmetrical purple reticular spots surrounding deflorescence areas. In rare cases, pyoderma gangrenosum can occur [7].

In laboratory diagnostics, the key procedure is the detection of ANCA in the blood. In the range of the known target molecules, proteinase-3 (PR3) is most often detected in GPA [4, 8]. ANCA detection using contemporary laboratory methods not only confirms the diagnosis but also has practical value, as it is the systemic vasculitis associated with PR3-ANCA that responds best to therapy regimens with genetically engineered biological drugs [5].

Morphological research methods are extremely important to confirm the genesis of skin lesions. In 50% of cases, the changes in GPA described earlier are caused by leukocytoclastic vasculitis of the dermis small vessels (capillaries, arterioles, and venules) with fibrinoid necrosis of the wall. According to the results of the study of biopsies, the combination of this phenomenon with the formation of perivascular granulomas is detected less often in the skin than in the internal organs. Histological examination of the skin in GPA reveals nonspecific perivascular lymphocytic infiltrates. Direct immunofluorescence can detect deposits of IgM and C3 component of complement around the dermis vessels in approximately 70% of cases [7].

Skin lesions in GPA usually occur during periods of disease exacerbation in a chronic recurrent course, last from several weeks to several months, and are resolved with systemic therapy [8]. Systemic therapy of ANCA-AV starts with inducing remission, the standard scheme of which, used since the 1970s, involves the prescription of systemic therapy with glucocorticoids (GC) (daily dose of 1 mg per 1 kg of body weight) in combination with cyclophosphamide according to the CYCLOPS protocol, achieving remission in more than 80% of cases [9, 10]. Such an aggressive therapeutic approach (undoubtedly associated with a high risk of adverse reactions) is chosen based on the data indicating a radical decrease in the life expectancy of patients with active GPA without treatment, averaging

6 months from the diagnosis establishment (more than 80% of patients die 3 years after the onset of the first symptoms). In turn, with the use of GC monotherapy, the inflammation activity can be reduced without significant influence on the survival rate of patients (12.5 months from the diagnosis establishment) [10].

GC therapy causes multiple adverse events, including skin manifestations represented by skin thinning, striae, purpura (1%–10%), and panniculitis (less than 1%), with an increased susceptibility to various infections [1]. The need to prescribe such a large volume of ANCA-AV immunosuppressive therapy is increasingly being discussed. Thus, as of today, a daily dose limit of up to 60 mg (in special cases up to 80 mg) prednisolone has been established, and the start time and rate of GC dose reduction have been accelerated significantly to reduce the total steroid load [10, 11].

In addition, the results of the PEXIVAS study demonstrated the equal efficacy of prescribing both full and reduced doses of GC (0.5 mg/kg per day) for induction therapy of severe ANCA-AV [12], which may become a serious reason for revising traditional therapy regimens to reduce the risk of adverse reactions to systemic GC therapy while maintaining equivalent efficacy.

However, despite the progress made, the risks of complications of combination immunosuppressive therapy, in particular the development of infections, are still high. The EUVAS study showed that 24% of ANCA vasculitis patients had infectious complications in the first year of the disease, with an infection-associated mortality rate of 5.6% [13]. French researchers found that 39.6% of ANCA-AV patients had episodes of infections in the first after diagnosis establishment, and 89% of serious infectious complications occurred during the period of treatment with GC in various dosages [14]. These data are consistent with the results of a study of the Chinese ANCA-AV patients, wherein 34.7% of patients had episodes of infections, 73.8% of which occurred during the induction therapy (with a median of 1.5 months from its start). In addition, infectious complications were detected in 38.5% of cases of GC monotherapy and 39.0% of patients who underwent combination therapy (GC and intravenous infusion of cyclophosphamide) [15]. In addition, because of the equal number of infection frequencies in the regimens using both

cyclophosphamide and rituximab, these risks could be most associated with the use of GCs [16].

The most common localization of the infectious process in patients with all forms of ANCA-AV is the lungs, with the following most common respiratory pathogens: *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*. Among the fungi, the most common opportunistic pathogen, *Pneumocystis jiroveci*, causes pneumocystis pneumonia (0.85%–12.00% of ANCA-AB cases). The second most frequent localization is the skin and underlying soft tissues. In relation to respiratory infectious complications, primary prevention measures have been developed, namely, the use of antistreptococcal and influenza vaccines or the preventive administration of co-trimoxazole for the period of treatment with cyclophosphamide. However, the only way to avoid severe secondary infection of eruptive elements is regular follow-up of the patient and a thorough clinical examination [16, 17].

The abovementioned text is confirmed by the clinical case given below, describing the generalized form of GPA with the dominance of skin lesions complicated by the infection.

An elderly 64-year-old woman was treated at the clinic of the Research Institute of Rheumatology and Allergology of the First Pavlov Saint Petersburg State Medical University. The patient complained of painful ulcers on the mucous membranes of the tongue and genitals, the skin of the scalp, lower extremities, elbow joints, and inframammary folds with sanioserous discharge and putrid odor, yellowish frothy nasal discharge with blood streaks, and unmotivated loss of body weight by up to 10 kg within 2 months.

Five months before hospitalization, the patient discovered a dark itchy spot under the right mammary gland with moderate liquid discharge; she used independently topical therapy (Solcoseryl, topical steroids) without a positive effect and therefore visited a mammologist surgeon. Excision of the skin defect was performed, followed by a histological examination of the material, which revealed a pronounced lymphoplasmacytic and neutrophilic infiltration of connective tissue in the bottom of the ulcer as well as infiltration by giant multinucleated cells, such as Pirogov-Langhans foreign bodies, which corresponded to subacute skin ulcers of the mammary gland with nongranulomatous productive

and exudative inflammation in the bottom and on the periphery without signs of tumor growth.

After 4 weeks, the patient noted similar lesions under the left mammary gland and behind the left ear. When a cytological examination of the discharge from the skin defect in the left parotid region was performed, no tumor cells were detected. Then, after another 4 weeks, painful nodules appeared in the scalp region, which increased in size and ruptured with the formation of ulcers as well as ulcerative defects on the mucous membranes of the lips, tongue, genitals, and skin of the upper and lower extremities with sanioserous discharge.

Examination at a dermatovenerologic dispensary during this period revealed leukocytosis (up to $12.6 \times 10^{12}/l$), increased erythrocyte sedimentation rate (ESR) (up to 96 mm/h), C-reactive protein (CRP) level up to 325.6 g/l, and *Staphylococcus epidermidis* in repeated microbiological examinations of skin scrapings. No organ lesions were found at the moment, and for the first time, systemic vasculitis with ulcerative-necrotic lesions of the skin was suspected; therefore, intravenous administration of 4 mg/day dexamethasone was started. In the 7 days of therapy, complaints of an increase in body temperature up to 38 °C and rare unproductive cough were noted. According to the chest X-ray results, infiltration in the lingular lobe of the left lung was found, and specific damage to the lung tissue was ruled out; within 3 days, no infiltration was found in the lung. Taking into account skin abnormalities, antibiotic therapy with doxycycline and azithromycin and topical treatment with metronidazole were performed. The patient was discharged with a recommendation of 40 mg/day oral prednisolone. During treatment, no changes were noted in her condition; therefore, she was hospitalized at the First St. Petersburg State Medical University.

The physical examination revealed second-degree obesity (body mass index 36.05 kg/m², height 158 cm, weight 90 kg). Edema of the lower extremities to the level of the knee joints was found, mainly on the left. Upon examination, the skin and visible mucous membranes were normal in color and moisture. On the skin of the lower third of the left lower leg, single extensive ulcerative defects (up to 10 cm in diameter) were noted, covered with black scab, with an inflammatory ridge in a circle (Fig. 1). A similar ulcer (up to 6 cm in size) was located in the area

of the left inguinal fold and of the outer labia. On the skin of the inner thigh surface, scalp, and above the elbow joints, multiple lesions (up to 1 cm in diameter), covered with hemorrhagic-necrotic crusts, were also revealed. In the area of the folds of the mammary glands and the sacrum, deep ulcers with a sanioserous discharge and putrid odor (Fig. 2, 3) were seen, and in the left parotid region, an ulcerative defect (3 cm in diameter) with putrid odor (Fig. 4) was noted. Examination of the mucous membrane of the tongue and upper lip also showed defects (up to 2 cm in size) without plaque. Convincing physical data in favor of damage to the cardiovascular, nervous systems, as well as signs of abdominal pathology, were not identified.

The laboratory studies revealed leukocytosis up to $15 \times 10^9/L$, an increase in ESR up to 104 mm/h, an increase in the level of CRP up to 94.7 mg/L and urea up to 8.3 mmol/L, and no increase in the level of creatinine (0.057 mmol/L; the glomerular filtration rate according to the CKD-EPI formula was 94.4 ml/min per 1.73 m²). Urinalysis revealed microhematuria (altered erythrocytes, 10–15 cells in the field of view; non-lysed erythrocytes, 8–15 cells in the field of view) and proteinuria (up to 0.19 g/day). The study of immunological markers revealed no antinuclear factor, and an increase in the ANCA titer to 1:640 (at a rate of less than 1:40) with a cytoplasmic type of luminescence was noted.

According to the computed tomography of the chest organs, a site of induration of the lung tissue in the V segment of the left lung, as well as a linear site of pneumofibrosis in the basal segment of the left lung, was revealed. At the same time, cavitary abnormalities were not seen in the lung tissue. The otorhinolaryngologist found ulcerative formations of the oral cavity, which was regarded as manifestations of systemic vasculitis. Taking into account the stable condition, the absence of an increase in renal dysfunction, and the high risk of infectious complications in the presence of multiple necrotic skin abnormalities with suppuration, the nephrologist decided to refrain from urgent renal biopsy.

The bacteriological examination of the ulcer discharge with the determination of sensitivity to antibiotics revealed secondary infection of ulcerative defects caused by *P. aeruginosa* and *S. epidermidis* with extensive resistance to antibiotics. A histological study of a biopsy sample of



Fig. 1. Crusted ulcerative defects of the left shin

Рис. 1. Покрытые струпом язвенные дефекты левой голени



Fig. 2. Weeping ulcer in the left inframammary fold

Рис. 2. Язва с мокнутием в области складки правой молочной железы



Fig. 3. Fibrin-covered ulcer in the sacral region

Рис. 3. Язва в области крестца, покрытая фибрином



Fig. 4. Ulcer with detritus behind the left ear

Рис. 4. Язва в левой заушной области с детритом

a musculocutaneous flap revealed an epidermis with signs of atrophy, dermis with edema, sclerosis, thin-walled vessels with swelling of endothelial cells having single lymphocytes around some of them, and small vessels of the hypodermis and connective tissue layers of skeletal muscle with thickened walls due to the proliferation of smooth muscle cells and moderate fibrosis. A biopsy of the buccal mucosa was also performed with subsequent histological examination following the detection of stratified squamous epithelium with signs of parakeratosis, minimal dyskeratosis, and foci of dystrophic cell changes with a focus of infiltration with neutrophilic granulocytes.

Thus, in accordance with the 1990 ACR classification criteria (a combination of sanguinopurulent discharge from nose and oral ulcers, computed tomographic signs of pulmonary involvement, and laboratory signs of kidney damage (microhematuria, moderate proteinuria)), the diagnosis of GPA associated with ANCA was reliable. The involvement of the lungs and kidneys in the process indicated a generalized form of the disease. In the clinical presentation, the

presence of generalized ulcerative-necrotic signs in the skin and mucous membranes, which confirm systemic vasculitis with secondary infection of ulcerative defects, was the most significant. The BVAS activity index was 23 points, which indicated a high degree of activity.

Given the high risk of septic conditions, standard cytostatic therapy was postponed until the foci of infection were eliminated. The dose of GC was adjusted at the rate of 1 mg/kg of body weight; antibiotic therapy was prescribed, taking into account the result of bacteriological research (intravenous meropenem 1 g thrice a day and vancomycin 1 g twice a day for 14 days) as well as topical antibiotic therapy (treatment of ulcerative skin defects with chlorhexidine, Sulfargin ointment, application of ointment with bacitracin and neomycin to the nasal mucosa).

During the therapy, positive changes were noted, namely, ulcerative defects were purified of purulent contents with their granulation, some of the ulcers under the scab were healed, new eruptive elements did not emerge, and laboratory inflammatory activity decreased (ESR 9 mm/h,

CRP 25.7 mg/l, leukocytes $9.9 \times 10^9/l$). The patient was discharged in a satisfactory condition with detailed recommendations to continue treatment under the case monitoring by a rheumatologist.

In this clinical case of GPA, a common triad consisting of damage to the kidneys, lungs, and upper respiratory tract without a pronounced dysfunction of vital organs was noted, while the first and most significant clinical manifestation of the condition was skin-necrotic changes. Despite the administration of a mildly reduced dose of GC at the stage of empirical treatment without using a cytostatic agent, secondary infection of skin defects with the nosocomial flora occurred, which caused the change in the clinical presentation, maintained the severity of inflammation, and limited the complete treatment of vasculitis.

The delayed prescription of cytostatic therapy, associated with the need to sanitize the foci of infection, can undoubtedly complicate the achievement of remission and, as a consequence, worsen the prognosis, but the priority of patient management is safety; therefore, the case follow-up of ANCA-AV patients during immunosuppressive therapy should also be considered mandatory regardless of the volume of the latter.

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