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Case report

On the issue of the syndromic forms of pyoderma gangrenosum

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ABSTRACT

Gangrenous pyoderma is an autoinflammatory polygenic neutrophilic dermatosis characterized by the formation of painful ulcerative skin defects with boldly raised undercut edges of purplish-cyanotic coloration and an erythema zone around the focus.

Gangrenous pyoderma can manifest as an isolated dermatosis, and be associated with various autoinflammatory syndromes: PASH (gangrenous pyoderma, conglobate acne and purulent hydradenitis), PAPA (gangrenous pyoderma, pyogenic arthritis and conglobate acne), PAPASH (gangrenous pyoderma, pyogenic arthritis, conglobate acne and purulent hydradenitis), PAPASC (gangrenous pyoderma, pyogenic arthritis, conglobate acne, purulent hydradenitis and ulcerative colitis), etc.

A number of genetic mutations have been found in the syndromic forms of gangrenous pyoderma (*MEFV*, *NOD2*, *LPIN2*, *NLRP3*, *NLRP12*, *PSMB8*, *MVK*, *IL1RN*, *PSTPIP1*) affecting inflammatory regulatory proteins, which contributes to the development of an autoaggressive process. Neutrophilic autoinflammatory syndromes have a common pathogenesis mechanism, which is an excessive activation of the innate link of the immune system, with hyperproduction of proinflammatory IL-1, IL-17 and chemokines, leading to aseptic neutrophilic inflammation of the skin.

At the moment, the treatment of syndromic conditions remains a difficult task. Systemic glucocorticosteroids, immunosuppressants, antimetabolites, and sulfone preparations are used in complex therapy, however, more and more studies indicate the possibility of therapy with genetically engineered biological drugs with TNF inhibitors, IL-1 and IL-17.

We present two clinical observations of rare forms of autoinflammatory neutrophilic syndromic conditions PASH and PAPASC in patients aged 20 and 21 years.

Keywords: gangrenous pyoderma; PASH syndrome; PAPASH syndrome; PAPAS syndrome; autoinflammatory neutrophilic syndromes.

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Клинический случай

К вопросу о синдромальных формах гангренозной пиодермии

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АННОТАЦИЯ

Гангренозная пиодермия — аутовоспалительный полигенный нейтрофильный дерматоз, характеризующийся образованием болезненных язвенных дефектов кожи с валикообразными приподнятыми подрытыми краями багрово-синюшной окраски и зоной эритемы вокруг очага.

Гангренозная пиодермия может проявляться изолированным дерматозом, а также быть ассоциированной с различными аутовоспалительными синдромами: PASH (гангренозная пиодермия, конглобатное акне, гнойный гидраденит), PAPA (гангренозная пиодермия, пиогенный артрит, конглобатное акне), PAPASH (гангренозная пиодермия, пиогенный артрит, конглобатное акне, гнойный гидраденит), PAPASC (гангренозная пиодермия, пиогенный артрит, конглобатное акне, гнойный гидраденит, язвенный колит) и др.

Обнаружен целый ряд генетических мутаций при синдромальных формах гангренозной пиодермии (*MEFV*, *NOD2*, *LPIN2*, *NLRP3*, *NLRP12*, *PSMB8*, *MVK*, *IL1RN*, *PSTPIP1*), затрагивающих белки-регуляторы воспаления, что способствует развитию аутоагрессивного процесса. Нейтрофильные аутовоспалительные синдромы имеют общий механизм патогенеза, представляющий собой чрезмерную, приводящую к асептическому нейтрофильному воспалению кожи активацию врождённого звена иммунной системы с гиперпродукцией провоспалительных интерлейкинов (IL) 1, 17 и хемокинов.

На сегодняшний день лечение синдромальных состояний остаётся трудной задачей. В комплексной терапии используют системные глюкокортикоиды, иммунодепрессанты, антиметаболиты, препараты сульфонового ряда, однако всё чаще результаты научных работ указывают на возможность терапии генно-инженерными биологическими препаратами — ингибиторами фактора некроза опухоли альфа (TNF-α), IL-1 и IL-17.

Представляем два клинических наблюдения редких форм аутовоспалительных нейтрофильных синдромальных состояний PASH и PAPASC у пациентов в возрасте 20 лет и 21 года.

Ключевые слова: гангренозная пиодермия; PASH-синдром; PAPASH-синдром; PAPASC-синдром; аутовоспалительные нейтрофильные синдромы.

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BACKGROUND

Gangrenous pyoderma is a rare neutrophilic dermatosis characterized by painful fast-growing ulcers with a purplish-cyanotic roller-like edge [1].

Its pathogenesis is poorly understood: gangrenous pyoderma is an autoinflammatory disease caused by impaired regulation of the innate immune system with overexpression of interleukin (IL)-1b, IL-8, IL-6, IL-16, IL-17, IL-23, IL-36, tumor necrosis factor alpha (TNF-α), and chemokines 1, 2, 3, and 16 [2].

At the onset of the disease, a papule, pustule, or bubble forms on the skin, the opening of which leads to the formation of a painful fast-growing ulcer with raised edges [1, 3].

Gangrenous pyoderma can be isolated or associated with systemic conditions (i.e., joint diseases, inflammatory bowel diseases, and lymphoproliferative blood diseases) or occur in the context of autoinflammatory syndromes such as PAPA (i.e., pyogenic arthritis, gangrenous pyoderma, and acne conglobata), PASH (i.e., gangrenous pyoderma, acne, and hidradenitis suppurativa), PAPASH (i.e., gangrenous pyoderma, pyogenic arthritis, acne, and suppurative hidradenitis), PsAPASH (i.e., psoriatic arthritis, gangrenous pyoderma, pyogenic arthritis, acne, and suppurative hidradenitis), PAC (i.e., gangrenous pyoderma, acne, and ulcerative colitis), and PASS (i.e., gangrenous pyoderma, acne, and ankylosing spondylitis) [4].

From a pathophysiological point of view, neutrophilic dermatoses are characterized by high levels of pro-inflammatory cytokines, chemokines, and other damaging effector molecules, as in autoinflammatory syndromes [5, 6]. This indicates that autoinflammatory syndromes and neutrophilic dermatoses have common pathological mechanisms associated with the activated innate immune system, wherein defects are noted in cellular signaling pathways regulated by mechanisms associated with inflammasomes, which produce pro-inflammatory IL-1, IL-17, and other effector molecules [7].

Common genetic markers have been identified in the syndromic forms. Mutations in the *NLRP3*, *PSTPIP1* (*CD2BP1*), *NOD2*, *MEFV*, and/or *NCSTN* genes have been shown to be associated with PASH syndrome. Genetic markers of suppurative hidradenitis are noted in PASH syndrome, such as mutations in the genes *MEFV*, *NOD2*, *LPIN2*, *NLRP3*, *NLRP12*, *PSMB8*, *MVK*, *IL1RN*, and *PSTPIP1*, as well as a permanent inflammatory profile with overexpression of IL-1b, IL-17, TNF-α, IL-8, CXCL1/2/3, and CXCL16; with SAPHO syndrome (i.e., synovitis, acne, pustulosis, hyperostosis, and osteitis), a combination of *NOD2* and *LPIN2* mutations and *PSTPIP1* is observed [8, 9].

Gangrenous pyoderma, suppurative hidradenitis, conglobate acne, palmar–plantar pustulosis, inflammatory bowel diseases (including Crohn's disease and ulcerative colitis), and musculoskeletal disorders (e.g., arthritis, synovitis, osteitis, hyperostosis, and axial spondyloarthropathy) are the most common diseases/clinical signs that occur in syndromic cases of gangrenous pyoderma (Table 1) [10]. In recent years, the so-called autoinflammatory march has often been mentioned, in which acne manifests first, followed by suppurative hidradenitis and gangrenous pyoderma [11]. Depending on the activity of the manifestations of diseases that develop into a syndrome, the patient can contact various specialists — a rheumatologist, gastroenterologist, dermatologist, or surgeon.

A four-step algorithm is proposed to accurately identify the syndromic form of gangrenous pyoderma (Fig. 1).

Gangrenous pyoderma in syndromic forms manifests as a single or multiple painful ulcers with purple roller-like raised undercut edges, with hyperemia along the periphery.

Purulent hidradenitis is a chronic recurrent dermatosis with elements of autoinflammation, lasting at least 6 months, characterized by the appearance of inflammatory nodules with purulent discharge, prone to the formation of fistulous passages and "cord-like" scars, which are mostly hypertrophic [12, 13]. The Hurley classification identifies three stages of the disease: I, the presence of one or more isolated abscesses without scars or sinuses; II, the presence of recurrent abscesses localized in more than one anatomical area and formation of sinus passages; and III, the presence of extensive abscesses with many interconnected sinuses, leading to the formation of scars.

In the classification of Van Der Zee and Jemec, six phenotypes of suppurative hidradenitis are distinguished: habitual, frictional furuncle, scarring folliculitis, conglobate, ectopic, and syndromal [14, 15]. To identify the syndromic forms of gangrenous pyoderma, patients should undergo laboratory tests (i.e., general and biochemical blood tests and glycated hemoglobin, protein electrophoresis, and rheumatological tests), histological examinations (i.e., biopsy from the marginal zone of gangrenous pyoderma), and tests that determine associated and inflammatory diseases (i.e., lung X-ray, colonoscopy, calprotectin examination for the diagnosis of Crohn's disease and ulcerative colitis, abdominal and pelvic ultrasound, chest computed tomography, and T-spot for the diagnosis of tuberculosis). Depending on the results of the examination, a consultation with a rheumatologist, gastroenterologist, or endocrinologist is scheduled.

The algorithm for determining the syndromic form of gangrenous pyoderma is based on a four-stage questionnaire on the most common symptoms of syndromic forms of gangrenous pyoderma, starting with gangrenous pyoderma, conglobate acne (A), and suppurative hidradenitis (SH,) and the identification (at the fourth stage) of axial spondyloarthritis (S), psoriatic arthritis (PsA), pyogenic arthritis (PA), ulcerative colitis (C), Crohn's disease (CD), or leukocytoclastic vasculitis (V).

Syndromal forms of gangrenous pyoderma are rare conditions and, according to recent data, commonly begin in childhood with recurrent arthritis or early onset of clinical signs of acne. After age 30 years, articular symptoms

Table 1. Syndromal forms of suppurative hidradenitis and gangrenous pyoderma

Syndromal forms of gangrenous pyoderma and suppurative hidradenitis										
Clinical symptoms	**Abbreviations adopted**				**Suggested abbreviations**					
	PASH	**PAPASH**	**PsAPASH**	**PASS**	**PAPASC**	**VPASH**	**PASCD**	**PASC**	**PAASCH/ PSC**	**PsAPSC**
Psoriatic arthritis (PsA)	-	-	V	-	-	-	-	-	-	V
Pyogenic arthritis (PA)	-	V	-	-	V	-	-	-	V	-
Pyoderma gangrenosum (P)	V	V	V	V	V	V	V	V	-	V
Conglobate acne (A)	V	V	V	V	V	V	V	V	V	-
Suppurative hidradenitis (SH or S)	V	V	V	V	V	V	V	V	V	V
Ulcerative colitis (C)	-	-	-	-	V	-	-	V	V	-
Spondyloarthritis (S)	-	-	-	V	-	-	-	-	-	-
Leukocytoclastic vasculitis (V)	-	-	-	-	-	V	-	-	-	-
Crohn's disease (CD)	-	-	-	-	-	-	V	-	-	V
Autoimmune hepatitis / primary sclerosing cholangitis (H/PSC)	-	-	-	-	-	-	-	-	V	-

become less pronounced [16]. Studies found in PubMed for January 2024 on syndromic forms of gangrenous pyoderma are limited, indicating the significance of the presented cases.

Moreover, studies describing the PAPASC syndrome, which is characterized by gangrenous pyoderma, SH, acne, pyogenic arthritis, and ulcerative colitis, are few. It is assumed that there is a common etiopathogenetic mechanism and, more specifically, a trigger of inflammatory bowel diseases, which triggers a pro-inflammatory cascade and immune-mediated dysregulation, which forms the basis of various inflammatory conditions [17, 18]. In an analysis conducted by Gadelha et al. [19], 7 of 8 patients with PAPASH, PsAPASH, or PASS had a positive serological test for antibodies to the baker's yeast *Saccharomus cerevisiae* (ASCA) and showed signs of subclinical inflammation of the digestive tract and refractory course during immunosuppressive therapy. Additionally, increasing evidence emphasizes the association of chronic inflammatory skin diseases with specific changes in the gastrointestinal microbiome, confirming the cross-reference between skin and intestinal bacterial flora [18, 20]. Skin improvement after proctocolectomy has been described in the literature [21].

The second clinical case presents a patient with PASH syndrome. Recently, it was established that the clinical triad of PASH is an autoinflammatory syndrome [18], which can be distinguished from PAPA by the absence of pyogenic sterile arthritis [19, 20].

The treatment of patients with syndromic forms is challenging. Classical immunosuppression regimens, such as systemic glucocorticoids, azathioprine (e.g., glucocorticoid-sparing agent), dapsone, and isotretinoin, do not always induce satisfactory disease control [21]. The therapy for SH depends on the stage of the pathological process. According to the Hurley classification, at stage I, it is possible to perform treatment with topical agents, and at stage II, long-term courses of antibiotics (doxycycline, clindamycin, and rifampicin), systemic retinoids, and antiandrogenic drugs are required. Long-term use of synthetic retinoids (acitretin) is considered the most effective treatment method. Evidence on the use of dapsone, human immunoglobulin, is available. Hurley stage III is considered as an indication for biological therapy [22, 23] to prepare the patient for the final surgical treatment for foci of SH, possibly with plastic surgery.

In accordance with the pathological mechanisms, TNF-α antagonists infliximab and adalimumab were found to have a more significant effect in the treatment of gangrenous pyoderma and SH [24, 25]. In recent years, new therapies have been developed, and successful treatment with anti-IL-1 and anti-IL-17 have been reported [26, 27]. However, in the presence of inflammatory bowel diseases, anti-IL-17 is contraindicated [28].

Herein, clinical observations of patients with syndromic forms of SH are presented.

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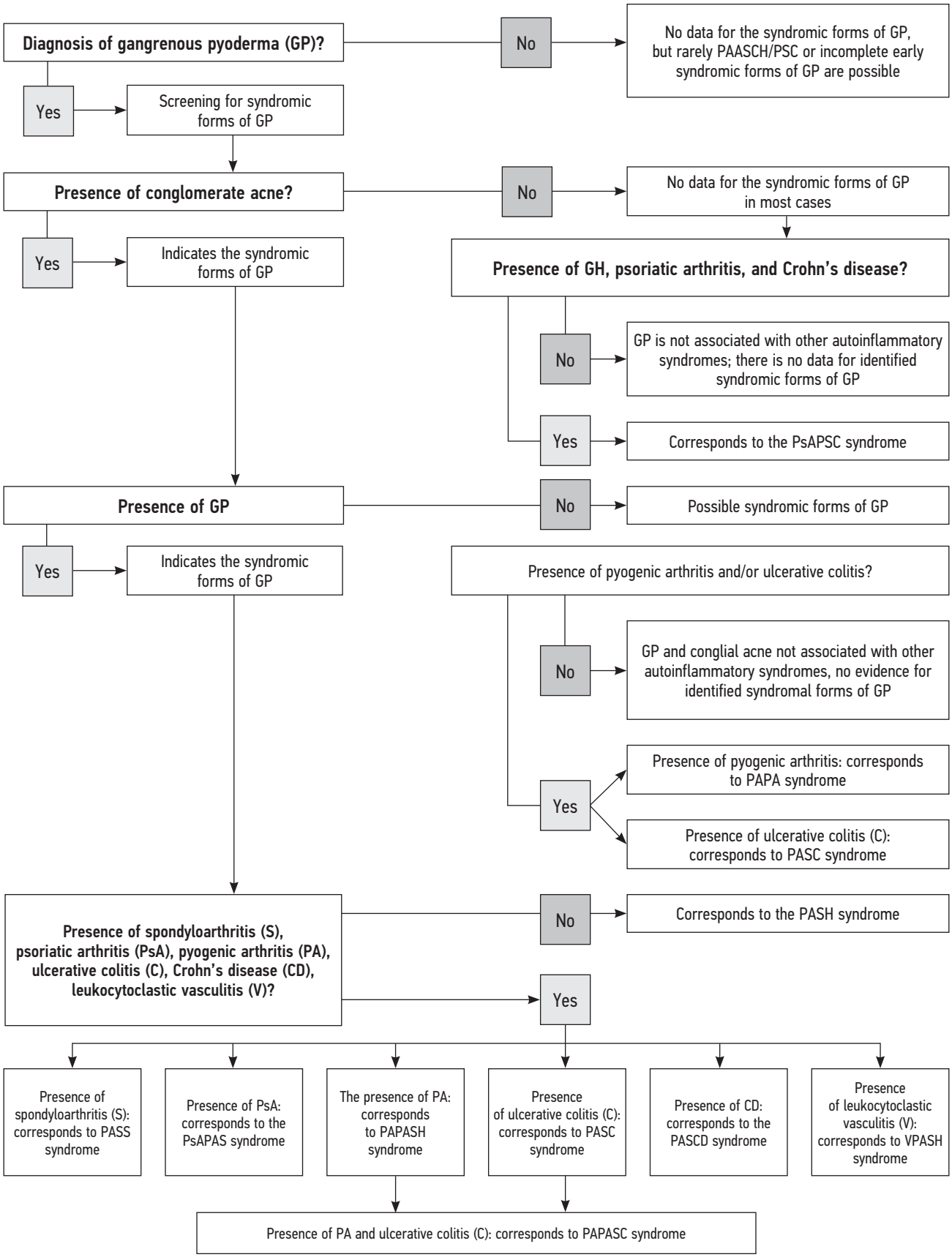


Fig. 1. A short guide (four-step algorithm) for the identification and determination of autoinflammatory syndromes associated with gangrenous pyoderma in clinical practice. SH, suppurative hidradenitis; GP, gangrenous pyoderma.

DESCRIPTION OF CASES

Clinical case 1

Patient K, 20 years old: In May 2023, patient K complained of ulcerative defects on the shins with pronounced painful sensations.

Anamnesis showed that the onset of the disease was in April 2017, which started with the appearance of rashes on the face, back, and chest. The patient sought consult with a dermatologist at his place of residence and was diagnosed with "conglobate acne." Isotretinoin (Sotret, 10 mg/day) was prescribed, but did not induce considerable effect; thus, patient K stopped taking the drug without doctor's advice. Following the skin manifestations, he began to experience pain in the sternum, collarbones, chest, ankle, and knee joints, accompanied by subfebrility. The patient consulted a rheumatologist and was diagnosed with juvenile ankylosing spondylitis, SAPHO syndrome. Methylprednisolone at a dose of 24 mg/day was prescribed, with positive dynamics characterized by significant reduction in the severity of the articular syndrome and regression of the skin process. Subsequently, gradual elimination of systemic glucocorticoids was recommended. Against the background of taking two methylprednisolone tablets, patient K noted recurrence of joint pain and resumption of acne. Hence, in August 2017, he was hospitalized in the rheumatology department, and therapy with the genetically engineered biological drug etanercept at a dose of 45 mg once a week was recommended. Consequently, a decrease in the severity of the articular syndrome was noted. However, the skin process periodically recurred; therefore, a course of therapy with isotretinoin (Roaccutane at a dose of 30 mg/day for 3 months) was reinitiated, with a positive response in the form of relief of inflammatory phenomena with an outcome in atrophic scars after acne.

In 2019, owing to an increase in calprotectin level in feces to 977 mcg/g and the presence of a colon lesion seen on colonoscopy, ulcerative colitis was diagnosed. Etanercept was then replaced with adalimumab at a dose of 40 mg once every 2 weeks. Against this background, pain symptoms in the joints regressed.

In August 2021, following adalimumab intake, the patient noted the simultaneous appearance of five ulcerative rashes on his thighs and shins, with purulent-hemorrhagic discharge, diagnosed as ecthyma. Prolonged (for 6 months) antibiotic therapy was provided without effect. In December 2021, the biopsy material was histologically examined. The epidermis had uneven thickness and was eroded in some areas and thickened in the preserved areas with pronounced acanthosis and hyper- and parakeratosis, and in the stratum corneum, accumulation of leukocytes with the formation of multiple pustules was observed. Furthermore, the dermis was sharply edematous, and a diffuse pronounced inflammatory infiltrate was noted, consisting mainly of neutrophils, spreading over the entire thickness of the dermis. Additionally, fragments of destroyed hair follicle and individual multinucleated cells were observed in the infiltrate.

In May 2022, owing to the emerging dermatosis, therapy with a genetically engineered biological drug was stopped. Nonsteroidal anti-inflammatory drugs were prescribed to relieve joint pain. After the withdrawal of adalimumab and following the use of antibacterial drugs, staphylococcal bacteriophage, topical combined steroid drugs, and regenerating ointments for ulcerative defects, positive dynamics was observed in the form of partial marginal scarring of ulcerative defects.

In November 2022, the patient presented to the V.A. Rakhmanov Clinic of Skin and Venereal Diseases of Sechenov University (Moscow). A differential diagnosis with SAPHO syndrome with paradoxical gangrenous pyoderma, PAPA syndrome (with confirmation of pyogenic arthritis), PASS syndrome (with confirmation of ankylosing spondylitis), or PsAPASH syndrome with or without palmar–plantar pustulosis (with confirmation of psoriatic arthritis) was made, and a study for the presence of the histocompatibility gene HLA-B27 was conducted. The test for HLA-B27 was negative.

In December 2022, complete scarring of ulcerative defects was noted following dapsone therapy at a dose of 50 mg 2 times a day 5 times a week, with a 2-day break and subsequent correction of the dosage of the drug, and antibiotic therapy with local application of topical combined steroids and agents stimulating tissue regeneration.

In January 2023, after suffering an acute respiratory viral infection, the patient noted ulcerative skin defects around the scars. He was then hospitalized at the V.A. Rakhmanov Clinic for Skin and Venereal Diseases, where he again received treatment with antibacterial drugs and staphylococcal bacteriophage with partial scarring of ulcers.

The actual aggravation occurred in April 2023 after a coronavirus infection, wherein the patient noted the appearance of two ulcerative defects on his shins and increased pain in the joints.

Local status upon admission (Status localis). The rashes were localized on the skin of both shins, represented by two ulcerative defects of various sizes (10–25 cm in diameter), with clear boundaries and purple raised edges along the periphery. The bottom of the ulcers was bright red with purulent-hemorrhagic exudate and areas of necrosis. Subjectively: pronounced soreness (Figs. 2*a* and 2*b*). Normotrophic scars were observed on the thighs and right shin; the scars were located at the same level with unchanged skin, up to 15 cm in diameter, with clear boundaries, dense on palpation, and pinkish red in color, and on the surface of which, skin atrophy was noted. Subjectively: no peculiarities (Figs. 3*c* and 3*d*). Multiple depigmented normal and atrophic scars associated with conglobate acne were found on the face, back, and chest. In the lumbar region, multiple striae were noted; they were located parallel to each other in the transverse direction of the back, represented by atrophic



Fig. 2. Patient K., 20 years old, PAPASC syndrome: *a* — ulcerative defect up to 20 cm in diameter on the skin of the right shin; *b* — ulcerative defect up to 10 cm in diameter on the skin of the left shin; *c* — normotrophic scar on the skin of the right shin; *d* — normotrophic scars on the skin of the thighs; *e* — normo- and atrophic scars associated with conglobate acne on the skin of the back, skin striae in the lumbar region; *f* — normo- and atrophic scars associated with conglobate acne on the skin of the face.

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stripes with uneven edges, measuring up to 10 cm in length and 1 cm in width, were pinkish purple in color (Figs. 2*e* and 2*f*).

Laboratory tests. Total blood count showed the following: erythrocytes, 4.8×10^{12}/l; hemoglobin, 140 g/l; hematocrit, 40%; platelets, 329×10^{9}/L; leukocytes, 13.74×10^{9}/L; lymphocytes, 59%; neutrophils, 50.5%; monocytes, 7.1%; eosinophils, 1.5%; basophils, 0.4%; sedimentation rate erythrocytes, 8 mm/h; and color index, 0.85. Biochemical blood test revealed the following: glucose, 5.16 mmol/l; total protein, 62 g/l; albumin, 38.1 g/l; urea, 7.0 mmol/L; uric acid, 215.50 mmol/L; creatinine, 69 mmol/L; total bilirubin, 10 mmol/l; direct bilirubin, 1.5 mmol/L; cholesterol, 3.2 mmol/ll; triglycerides, 0.41 mmol/L; high-density lipoproteins, 1.12 mmol/L; alanine aminotransferase, 26 units/L; aspartate aminotransferase, 24 units/L; lactate dehydrogenase, 132 units/L; alkaline phosphatase, 66 units/L; gamma-glutamyltransferase, 17 units/L; and C-reactive protein, 13.8 mg/l. General urinalysis results were as follows: color, yellow; specific gravity, 1.010; incomplete transparency; pH, 6; protein, negative; glucose, negative; ketones, negative; nitrites, negative; urobilinogen, normal; leukocytes, 3–6 in the field of vision; erythrocytes, negative; mucus, traces; and bacteria, traces. Coagulogram showed the following: activated partial thromboplastin time, 0.85; quick prothrombin, 96%; international normalized ratio (INR), 1.10; prothrombin time, 12.1 sec; and fibrinogen, 3.62 g/l.

All laboratory test results were within the reference values. However, general blood test showed increased leukocyte and lymphocyte levels, and the biochemical blood test revealed a decrease in total protein and an increase in C-reactive protein.

Diagnosis. Considering the clinical picture and anamnestic data of the patient and based on the diagnoses of juvenile ankylosing spondylitis (in the rheumatology department) and conglobate acne (dermatologist at the place of residence) in 2017, ulcerative colitis in 2019, and gangrenous pyoderma in 2021, PAPASC syndrome was diagnosed (Fig. 3).

Treatment. In the dermatovenerology department, treatment with systemic steroids (prednisolone at a dose of 40 mg once a day with gradual reduction of the drug dosage) with appropriate corrective therapy, antibacterial agents, and topical bactericidal preparations was carried out. Currently, the patient is being treated at the V.A. Rakhmanov Clinic for Skin and Venereal Diseases.

Clinical case 2

Patient Sh, 21 years old: In June 2023, patient Sh was admitted with complaints of widespread rashes on the face, trunk, and extremities.

Anamnesis: The patient considered himself sick since the summer of 2021, when papular rashes first appeared in the area of his left ankle joint after swimming in a pond. After 2 weeks, he noted left foot swelling. The patient sought consult with a dermatologist at his place of residence and was prescribed with antibacterial drugs (the name of which he can not specify) with a temporary positive effect. In September 2021, he noted the appearance of open and closed comedones and acne on the face, trunk, and upper extremities and the spread of papular rashes with a necrotic center on the lower extremities. The dermatologist referred the patient to a rheumatologist. Behcet's disease was suspected, and blood test for HLA-B51 (positive), complement components C4 (0.39 g/l), C3 (1.66 g/l), and antibodies to nuclear antigens ANA (negative) was performed.

From January 2022 to February 2022, the patient was hospitalized in a rheumatology hospital because of ulcerative defects on his shins. He was treated with metipred at a dose of 16 mg/day, plaquenil at 200 mg/day, and vascular drugs. Moreover, a biopsy of the skin flap was performed, followed by histological examination, which showed pronounced uneven sclerosis in the dermis and integumentary multilayer

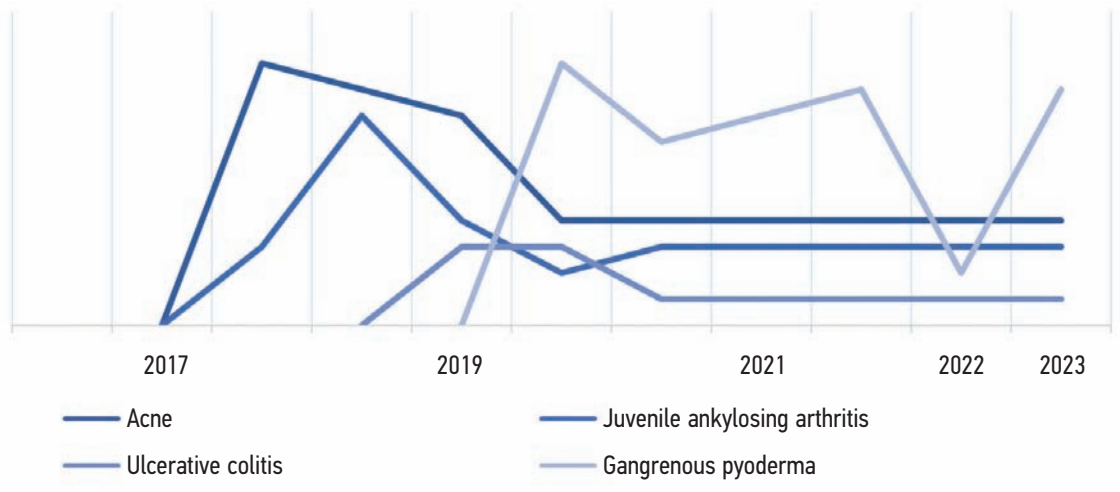


Fig. 3. Course of the disease in a patient with PAPASC syndrome.

squamous epithelium with phenomena of dystrophy and focal acanthosis in the area of inflammation, subepithelial sections, and dermis focal and dense leukocyte infiltration with thickening and microabsorption involving deep sections of the dermis, along the excretory ducts of appendages and subcutaneous adipose tissue to a lesser extent. In the vessels of small and medium caliber, pronounced lymphoplasmocytic infiltration involving all layers was observed, as well as vacuolization and proliferation of part of the endotheliocytes; a part of the vessels showed no visible changes. *Conclusion:* morphological picture and immunophenotype of vasculitis with lesions of medium and small vessels, with foci of subepithelial microabsorption and involvement of excretory ducts of skin appendages. The histological picture does not contradict the clinical diagnosis of Behcet's disease. Against the background of systemic therapy in the rheumatology department, a positive trend in the form of partial scarring of ulcers was noted.

In October 2022, after hypothermia, the patient was hospitalized again because of the appearance of ulcerous defects on the previously intact skin and in the same places as before. He was diagnosed with necrotizing nodular vasculitis of Werther type and treated with prednisolone at a dose of 30 mg orally with gradual reduction of the drug dose and topical steroids with a positive effect in the form of complete scarring of ulcerous defects. Prednisone was

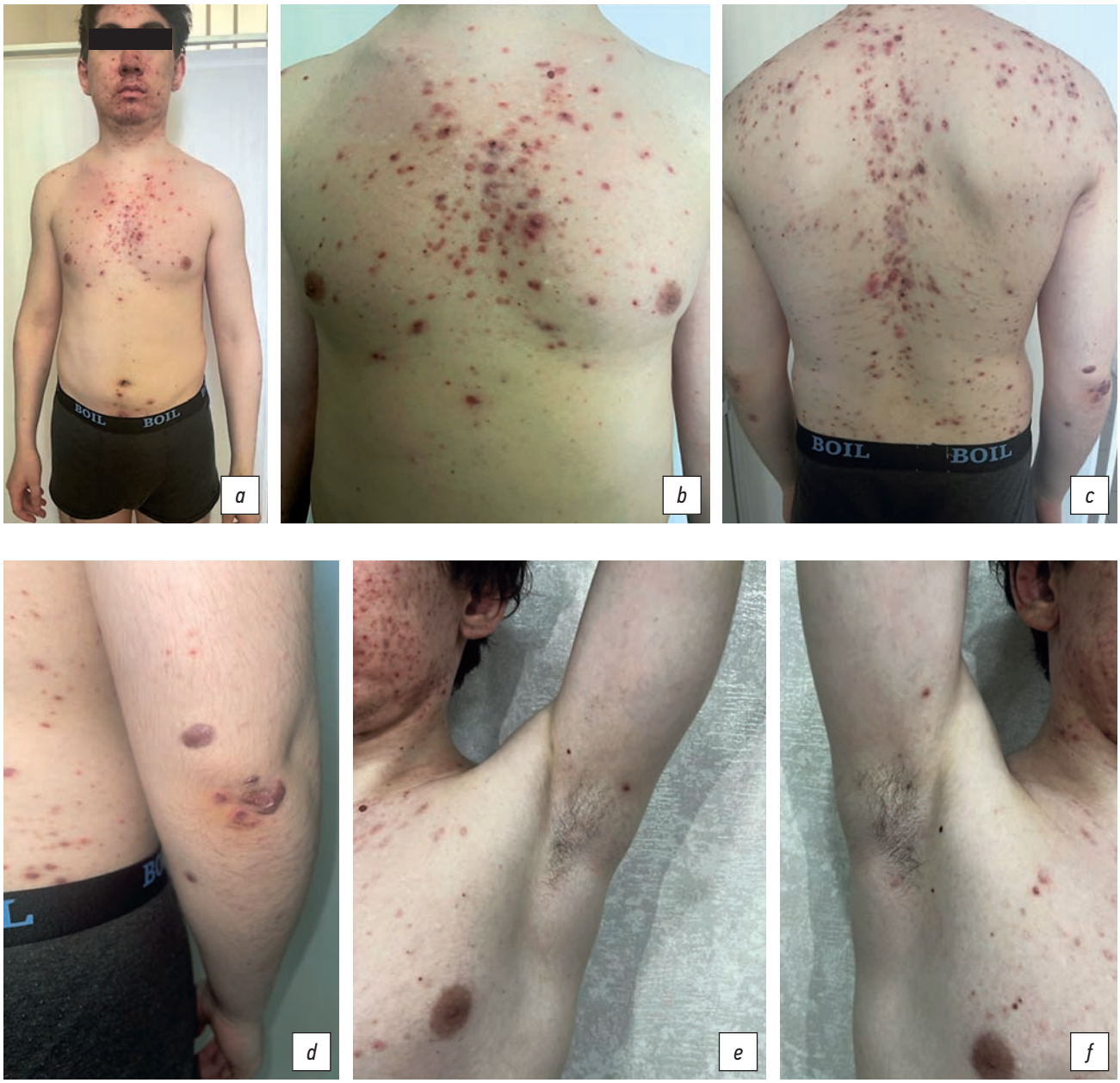


Fig. 4. Patient Sh., 21 years old, PASH syndrome: *a* — multiple rashes on the face, trunk; *b* — multiple rashes on the chest skin, post-acne scars; *c* — rashes on the back skin, single striae in the lumbar region; *d* — keloid scars on the skin of the elbows; *e*, *f* — single painful bruise-coloured nodules in the axillary region; *g* — hyperpigmented normotrophic scars on the skin of the lower legs (general view); *h* — multiple hyperpigmented normotrophic scars on the skin of the lower legs.

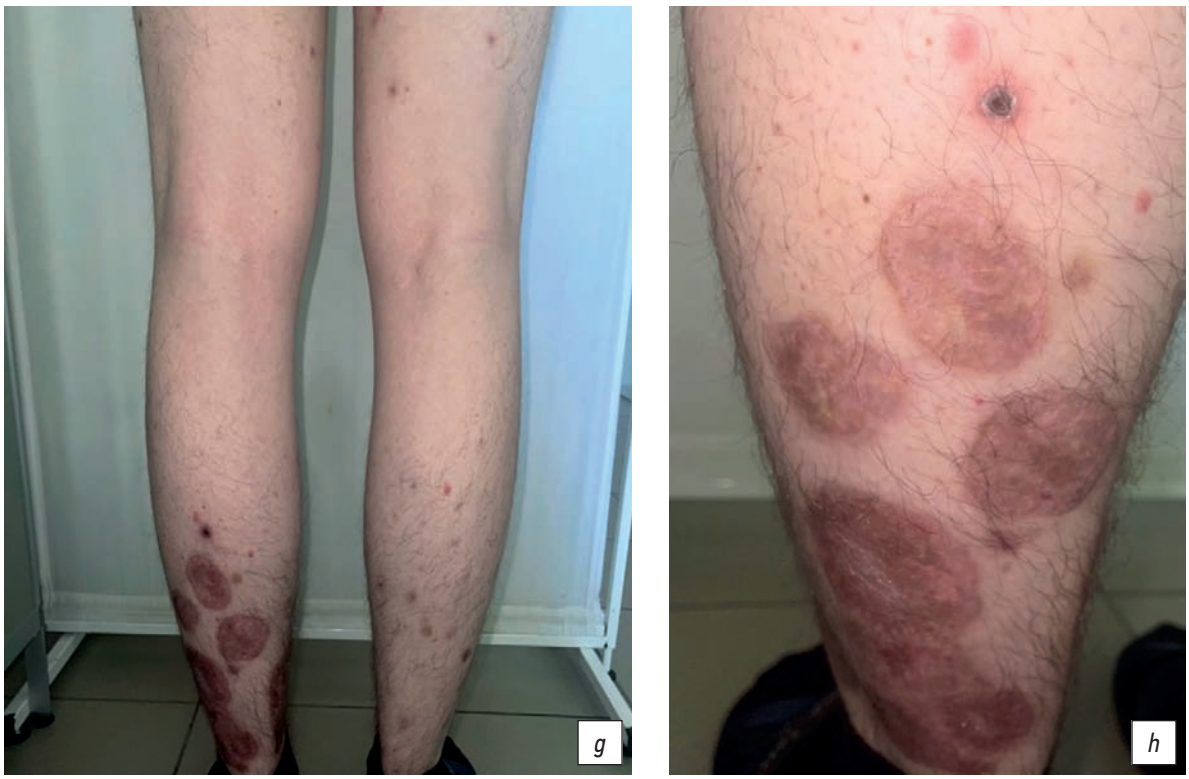


Fig. 4. The End.

continued for an indefinite period after reaching a dosage of 5 mg/day.

Further, the skin process was undulating in nature, with periods of exacerbation after hypothermia. The disease had an atypical course. Thus, in May 2023, the patient was re-admitted to the rheumatology department to verify the diagnosis and correct therapy. Owing to the absence of a history of lesions of the mucous membranes of the genital organs and oral cavity, a negative Patergia test, lacking data for diseases of the osteoarticular system, and signs of phlebitis, seen on ultrasound of the veins of the lower extremities, the diagnosis of Behcet's disease was excluded. In the hospital, the patient received methylprednisolone at 6 mg for 7 days with appropriate corrective therapy, plaquenil at 200 mg/day, and colchicine at 0.5 mg/day, with positive dynamics in the form of stabilization of the skin process. During hospitalization, hypercoagulation along the internal pathway of prothrombin formation was diagnosed owing to an increase in the D-dimer index, a decrease in the level of activated partial thromboplastin and prothrombin time, and a relative increase in fibrinogen levels. The course of therapy with systemic steroids, plaquenil, and oral anticoagulants was continued, as well as hospitalization at the V.A. Rakhmanov Clinic for Skin and Venereal Diseases to verify the diagnosis and correct therapy.

Local status upon admission (Status localis): A number of comedones, papules, pustules in various stages of development, numerous large nodules, and atrophic post-acne scars were found on the face, back, and chest (Figs. 4*a* and 4*b*). There were single striae on the lumbar region, located parallel to each other in the transverse direction of the back, represented by atrophic strips with irregular edges measuring up to 5 cm in length and 0.5 cm in width, with a pinkish purple color. Keloid scars up to 2 cm in diameter, red in color, and of dense consistency were noted in the elbow area (Figs. 5*c* and 5*d*). In the armpits and inguinal region, against the background of infiltration, single red painful nodes with a bluish tinge were noted (Figs. 5*e* and 5*f*). On the skin of the lower extremities, mainly the shins and ankle joints, multiple hyperpigmented normotrophic scars of rounded outlines with clear boundaries were observed (Figs. 4*g* and 4*h*).

Laboratory tests. Total blood count: erythrocytes, 4.89×10^{12}/l; hemoglobin, 156 g/L; hematocrit, 45%; platelets, 309×10^{9}/L; leukocytes, 9.14×10^{9}/L; lymphocytes, 42%; neutrophils, 50.1%; monocytes, 4.8%; eosinophils, 1.3%; basophils, 1.8%; sedimentation rate erythrocytes, 5 mm/h; and color index, 0.96. Biochemical blood analysis: glucose, 4.77 mmol/l; total protein, 79 g/l; albumin, 50.3 g/l; urea, 3.01 mmol/L; uric acid, 347.2 mmol/L; creatinine, 80 mmol/L; total bilirubin, 8.1 mmol/L; direct bilirubin, 1.4 mmol/L; cholesterol, 4.6 mmol/ll; triglycerides, 1.8 mmol/L; high-density lipoproteins, 1.38 mmol/L; alanine aminotransferase, 16 u/L; aspartate aminotransferase, 16 u/L; lactate dehydrogenase, 174 u/L; alkaline phosphatase, 105 u/L; gamma-glutamyltransferase, 19 u/L; and C-reactive protein, 4.2 mg/l. General urinalysis: color, yellow; specific gravity, 1.010; incomplete transparency; pH, 6; protein, negative;

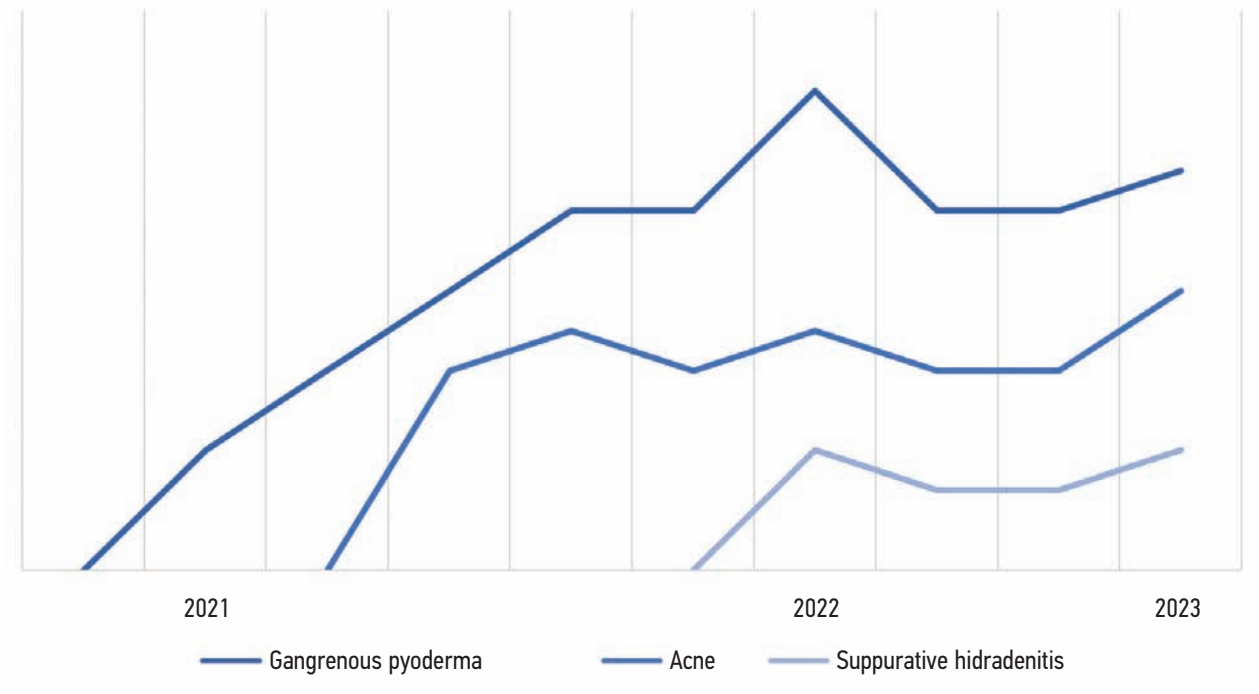


Fig. 5. Course of the disease in a patient with PASH syndrome.

glucose, negative; ketones, negative; nitrites, negative; urobilinogen, normal; leukocytes, 3–6 in the field of vision; erythrocytes, negative; mucus, negative; and bacteria, negative. Coagulogram: activated partial thromboplastin time, 1.1; quick prothrombin, 96%; INR, 1.23; prothrombin time, 13.5 sec; and fibrinogen, 3.26 g/l.

All indicators were within the reference values. However, an increase in INR and prothrombin time was observed on coagulogram, which is explained by taking anticoagulants.

Diagnosis. Based on the clinical picture, anamnesis data, and the results of histological examination, PASH syndrome was diagnosed, as well as based on the diagnoses of fulminant acne and gangrenous pyoderma (ulcerative defects on the skin of the legs) and SH (single recurrent nodes in the axillary and inguinal areas) (Fig. 5).

Treatment. In the dermatological department, the patient was recommended to continue treatment with oral corticosteroids with appropriate corrective therapy and hydroxychloroquine and oral anticoagulants prescribed at the V.A. Nasonova Scientific Research Institute of Rheumatology. At the V.A. Rakhmanov Clinic for Skin and Venereal Diseases, ceftriaxone at a dose of 1 g 1 time per day intramuscularly, no. 10, was added to the therapy, and owing to the torpid course of the skin process, a drug from the retinoid group, Aknecutan, was prescribed at a dose of 32 mg/day. However, on day 3 of taking isotretinoin, new rashes appeared on the patient's hips and shins, characterized by papules with a tendency of necrosis in the center. Thus, Aknecutan was stopped, and 2 ml of Dipromet was injected once intramuscularly, the dosage of systemic steroids was increased to 4 tablets per day, and acne therapy with topical drugs was limited (Differin gel in the morning and Klenzit C in the evening). A long course of antibacterial drug therapy, according to the scheme rifampicin at 300 mg 2 times a day and clindamycin at 300 mg 2 times a day for 12 weeks, was recommended.

Against the background of the therapy, positive dynamics was noted: the progression of gangrenous pyoderma was stopped and inflammation on the face, chest, and back improved.

DISCUSSION

The interest of these clinical observations is that different clinical conditions in syndromal forms of gangrenous pyoderma begin at different periods of life, and such patients may not be promptly seen by a dermatovenerologist, as these patients first consult general practitioners, surgeons, rheumatologists, and others. In this regard, such patients should be examined to exclude concomitant diseases.

During follow-up and further evaluation of patients, the syndromal form may change, and patients with the same diagnosis may have different manifestations of symptoms and responses to treatment.

The treatment of patients with gangrenous pyoderma with systemic glucocorticoids, azathioprine, dapsone, and isotretinoin does not always lead to a satisfactory result. Thus, in recent years, TNF-α antagonists, namely, infliximab and adalimumab, have been used, and practical medicine has presented successful treatment of such patients with anti-IL-1 and anti-IL-17. However, anti-IL-17 drugs are contraindicated in inflammatory bowel diseases.

Patients with syndromal forms of gangrenous pyoderma show significantly worsened quality of life, including social isolation because of extensive skin lesions and difficulties and limited available treatment options. Thus, timely diagnosis and appropriate pathogenetic treatment help improve the patient's clinical picture and quality of life.

CONCLUSION

The presented clinical cases indicate the variety of syndromic forms of gangrenous pyoderma and the difficulties of differential diagnosis and accurate diagnosis. Doctors' awareness of such cases is beneficial in the appropriate management of severe patients.

ADDITIONAL INFORMATION

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