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M.E. Zapolskiy, M.M. Lebediuk, I.V. Svistunov[1], M.O. Dudchenko[2],
N.B. Prokofyeva, O.V. Bachynska
Odessa National Medical University, Odessa, [1]National Medical Academy of Postgraduate Education named after P.L. Shupik, Kyiv, [2]Poltava State Medical University, Poltava

PATHOMORPHOLOGICAL ASPECTS OF PYODERMA GANGRENOSUM

e-mail: kdvonmu@hotmail.com

Pyoderma gangrenosum is a rare inflammatory skin disease of unclear etiology, characterized by neutrophilic infiltration of the dermis with tissue destruction. The pathogenesis of pyoderma gangrenosum has not been fully studied and the variety of clinical forms and difficulties in diagnosing this disease are a major problem for clinicians. Currently, the main diagnostic criterion is histological examination. The aim of our work was to analyze the staging of pathomorphological changes development in patients with pyoderma gangrenosum depending on the dynamics of clinical changes. In 21 histological samples of patients, specific histological markers were identified for each stage and clinical form. The most significant were intravascular fibrin deposition with subsequent development of fibrinoid necrosis, characteristic of earlier stages of the disease, formation of granulomas containing giant cells of foreign bodies characteristic of late necrotic stages of pyoderma gangrenosum. Eosinophilic microabscesses were an important histological feature of the vegetative forms of the disease.

Key words: gangrenous pyoderma, pathomorphology, histology, diagnosis

**М.Е. Запольський, М.М. Лебедюк, І.В. Свистунов, М.О. Дудченко,
Н.Б. Прокоф'єва, О.В. Бачинська**

ПАТОМОРФОЛОГІЧНІ АСПЕКТИ ГАНГРЕНОЗНОЇ ПІОДЕРМІЇ

Гангренозна піодермія це рідкісне запальне захворювання шкіри нез'ясованої етіології, що характеризується нейтрофільною інфільтрацією дерми з деструкцією тканин. Патогенез гангренозної піодермії до кінця не вивчений, різноманітність клінічних форм і труднощі діагностики цього захворювання є основною проблемою для клініцистів. На даний час основним діагностичним критерієм є гістологічне дослідження. Мета нашої роботи – проаналізувати стадійність розвитку патоморфологічних змін у хворих залежно від динаміки клінічних змін. У 21 гістологічному зразку хворих визначені специфічні гістологічні маркери для кожної стадії та клінічної форми. Найбільш значущими були внутрішньосудинні відкладення фібрину з подальшим розвитком фібриноїдного некрозу, характерного для ранніх стадій гангренозної піодермії, утворення гранульом, що містять гігантські клітини сторонніх тіл, характерні для пізніх некротичних стадій захворювання. Важливою гістологічною ознакою вегетативних форм гангренозної підермії були еозинофільні мікроабсцеси.

Ключові слова: гангренозна піодермія, патоморфологія, гістологія, діагностика

The study is a fragment of the research project "Improvement of algorithms of diagnosis, treatment, and prevention of chronic dermatoses, benign and malignant skin neoplasms", state registration no. 0121U113996.

Gangrenous pyoderma (PG – pyoderma gangrenosum) is a rare disease characterized by neutrophilic infiltration of the dermis and manifested in the form of inflammatory and ulcerative skin lesions [1, 8, 13].

Etiology. The etiology of PG remains unclear, but today PG is considered to be an autoinflammatory disease [11, 12]. Besides, the disease is often associated with inflammatory bowel processes (nonspecific ulcerative colitis, Crohn's disease), blood pathology, malignant neoplasms, arthritis, etc. [7, 11]. Pyoderma gangrenosum can also be caused by drugs such as granulocyte colony-stimulating factor (G-CSF), isotretinoin, propylthiouracil, sunitinib, gefitinib, imatinib, dapilumab, etc. [2, 12].

Pathophysiology. The pathophysiology of PG is not fully studied [2]. It is believed to include dysregulation of both the innate and adaptive immune responses, neutrophilic abnormalities, environmental and genetic factors [1, 5, 15]. A number of studies have shown that cytokines (IL-1β, IL-8, IL-17, TNF-α), matrix metalloproteinases (MMP-2, MMP-9), vascular endothelial growth factor (VEGF) and markers of inflammation play a role in the development of the disease [2, 9].

Thus, dysfunctions of inflammatory cytokines, immune system and neutrophils in combination with specific genetic mutations predispose patients to the development of this complex disease [4].

Clinical manifestations. PG symptoms usually develop after minor injuries in the form of single vesicles, nodules, erosions (the phenomenon of "patergy"). Later, a peripheral growth of lesions with the formation of an inflammatory cushion, often bleeding with minimal trauma is observed. In some cases, the central part of the erosions independently epithelizes, and the edges continue to ulcerate and necrotize, imitating a gangrenous process. Many patients already in the early stages of the disease note a burning sensation, tingling, severe pain in the lesions.

Clinical forms of PG are diverse and include the ulcerative, pustular, bullous, vegetative, peristomal and postoperative ones [5, 12]. Each variant has differences in the clinical picture.

Diagnostics. PG is a diagnosis by exclusion. The clinical, histological and laboratory findings are nonspecific [3, 6]. Examination of a patient with suspected PG should include case history, physical examination, skin biopsy, and laboratory examination.

Delphic Consensus of International Experts (2018) [10] proposed the following diagnostic criteria for ulcerative PG: 1 main criterion – biopsy of the ulcer edge, demonstrating neutrophilic infiltration, and 8 secondary criteria: (1) exclusion of an infection; (2) pathergy; (3) history of inflammatory bowel disease or inflammatory arthritis; (4) history of papules, pustules, or vesicles that are ulcerated within 4 days after appearing; (5) peripheral erythema, boundary violation and tenderness at the site of ulceration; (6) multiple ulcerations, at least 1 on the front of the lower leg; (7) scars in the shape of a mushroom or "wrinkled paper" on the healed areas of the ulcers; and (8) reduction in ulcer size within 1 month of starting immunosuppressive drugs.

Diagnostic criteria for bullous, pustular and vegetative PG forms were also proposed [14].

Thus, taking into account the difficulties in the clinical diagnosis of PG, histological examination remains the main diagnostic criterion. The results of the study make it possible to determine not only the PG phase and the severity of the inflammatory process, but also the intensity of neutrophilic tissue infiltration, which is important when choosing a therapeutic algorithm.

The purpose of the study was to analyze the staging of the development of the pathomorphological changes depending on the dynamics of clinical changes in patients with PG.

Materials and methods. We observed 21 patients with gangrenous pyoderma, including 8 men and 13 women during the period from 2011 to 2021. The age of the patients ranged from 26 to 73 years. All of them received treatment on the basis of the Department of Dermatology and Venereology of the Odessa National Medical University and the Regional Dermato-Venereological Center. In order to clarify the peculiarities of the course of certain forms of gangrenous pyoderma, a histological examination of tissues was performed directly in the affected areas of the lesion.

In 21 histological samples of patients, specific histological markers were identified for each stage and clinical form. The most significant were intravascular fibrin deposition with subsequent development of fibrinoid necrosis, characteristic of earlier stages of the disease, and formation of granulomas containing giant cells of foreign bodies characteristic of late necrotic stages of pyoderma gangrenosum. Eosinophilic microabscesses were an important histological feature of the vegetative forms of the disease. Pieces of biopsy tissue were fixed in a 10 % solution of cold neutral formalin (pH 7.4) for 24 hours, then poured into highly purified paraffin. From paraffin blocks on a rotary serial histological section with a thickness of 5±1 μm were made with a microtome, which was then stained with hematoxylin and eosin, Weigert's resorcin-fuchsin, with toluidine blue at pH 2.6 and 5.3, put the CHIK reaction with treatment control sections with amylase. Studies of drugs in transmitted light were carried out on a research microscope Olympus CX-41 with a digital video camera Olympus DP21 (Japan) connected to a personal computer.

The histological material from the peripheral foci of inflammation was taken by the surgeon of the dermatological department using a puncture biopsy. Informed consent was obtained from all the patients included in the study. The authors declare that all the procedures and experiments in this study comply with the ethical standards of the 1975 Declaration of Helsinki, revised in 2008, as well as national legislation.

Results of the study and their discussion. The most frequent manifestation of gangrenous pyoderma was the ulcerative form with localization on the lower extremities – in 13 (61.9 %) patients. Less common were the pustular (n=5, 23.8 %), vegetative (n=1, 4.8 %), and bullous forms (n=2, 9.5 %) of the disease. In most cases, the disease had a stable course, without any periods of stable remission.

In the development of the morphological picture, it was possible to trace the stages, corresponding to the dynamics of the clinical picture from a pustule to a deep ulcer.

The ulcerative form of gangrenous pyoderma. The initial histological changes were variable and depended on the time of the patient visit and biopsy sampling. Before the appearance of an ulcer in the clinical picture, acanthosis, a dense superficial infiltrate in the upper part of the dermis, especially in the papillae, consisting mainly of lymphocytes, monocytes, with an admixture of neutrophilic granulocytes, was found in the preparation (fig. 1A). Later there was an increase in exocytosis with the formation of intraepithelial abscesses in the epidermis (fig. 1B). With the growth of necrobiotic changes in the epidermis, edema of the dermis appeared and the number of neutrophilic granulocytes in its upper layers increased. At the same time, the structuredness of connective tissue fibers was lost, neutrophilic infiltration spread to all dermal zones with a significant increase in the papillary layer of the dermis (fig. 1C). Later, in patients

with pyoderma gangrenosum, there occurs necrotization of the epidermis and the upper part of the dermis with the formation of an ulcer in the clinical picture. At its edges, epidermal hyperplasia was noted up to pseudoepitheliomatous hyperplasia, the bottom of the ulcer was covered with necrotic masses and inflammatory elements, mainly neutrophilic granulocytes (fig. 1D).

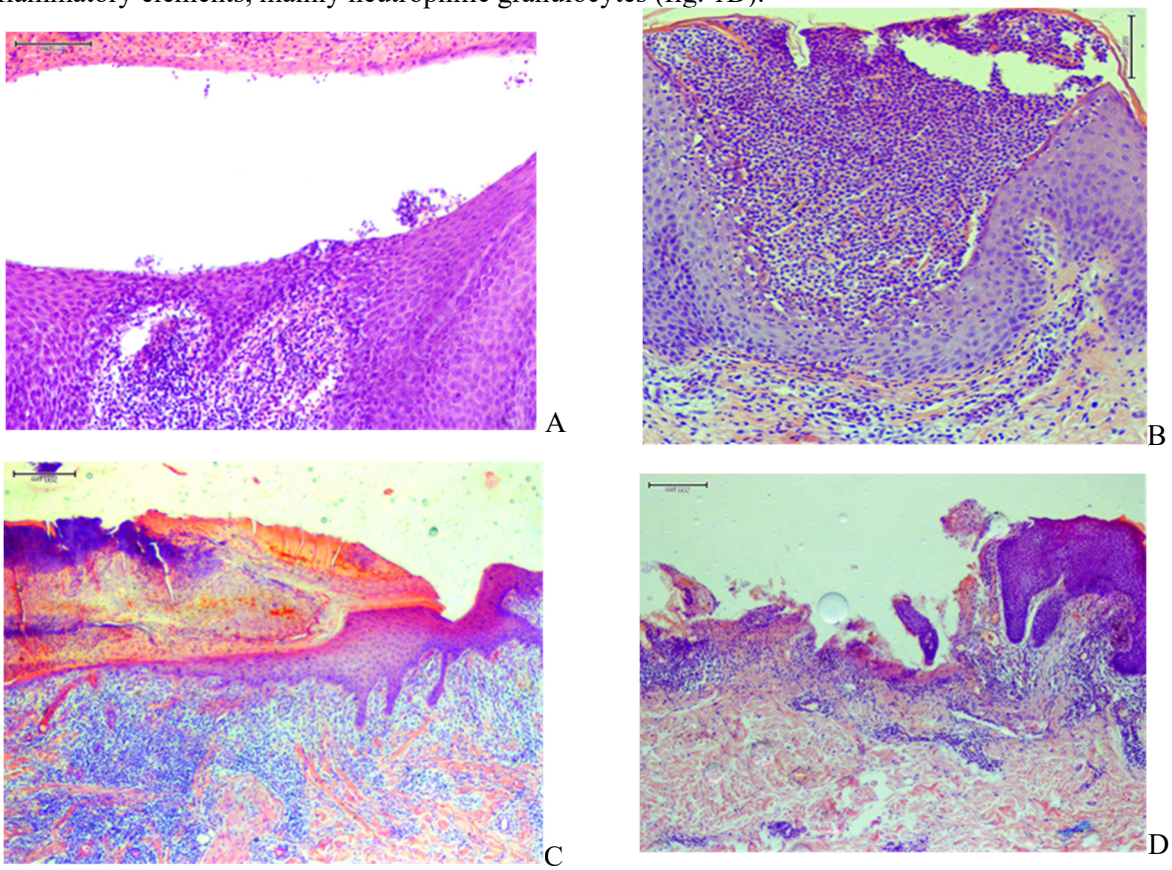

Fig. 1. Pyoderma gangrenosum. A – Acanthosis, subcorneal cavity formation and dense inflammatory infiltrate in the papillary dermis. Hematoxylin-eosin, × 100. B – Intraepithelial pustule. Hematoxylin-eosin, × 100. C – Acanthosis with symptoms of edema and the formation of a strip-like inflammatory infiltrate with an admixture of neutrophilic granulocytes in the upper dermis. Hematoxylin-eosin, × 40. D – Purulent-necrotic ulcer. Hematoxylin-eosin, × 40.

In the progression of the neutrophilic granulocytes accumulation process, abscesses were formed in the thickness of the dermis. The area of neutrophil accumulation slightly increases closer to the basal layer of the epidermis. A large number of damaged neutrophils is observed, which is a sign of impaired chemotaxis processes (fig.2A, fig. 2B). At the same time, an increase in the number of blood vessels with the phenomena of endothelial proliferation, infiltration of their walls by lymphocytes and neutrophilic granulocytes with intramural and intravascular deposition of fibrin was observed in the entire dermis, followed by the development of fibrinoid necrosis (fig. 2C) and melting of the vessel walls (fig. 2D).

In the middle and lower parts of the dermis, the infiltrate became chronic and consisted of lymphocytes, neutrophils, plasma cells, histiocytes, fibroblasts. At the same time, in some patients, epithelioid cells with the formation of granulomas were found in biopsy preparations, which, in some cases, contained giant cells of foreign bodies (fig. 3A).

In addition, in some patients, the infiltrate penetrated deep into the subcutaneous fat layer with the development of panniculitis (fig. 3B).

The most rare variants of gangrenous pyoderma include the bullous form. For this form of the disease, more characteristic histological changes are a poorly defined subepidermal or intraepidermal blister with epidermal necrosis and pronounced edema of the upper layer of the dermis with a predominance of neutrophilic granulocytes (fig. 3C).

In the pustular form of pyoderma gangrenosum, a dense dermal neutrophilic infiltrate (often concentrated around the follicle) with subepidermal edema and neutrophil infiltration into the epidermis with the formation of subcorneal pustules was observed (fig. 3D).

The histological picture of the vegetative form of gangrenous pyoderma was characterized by pseudoepitheliomatous hyperplasia, the formation of a sinus passage and palisade granulomas against the background of foci of dermal neutrophilic abscesses. For the vegetative form, the presence of eosinophilic microabscesses in the dermis is more characteristic.

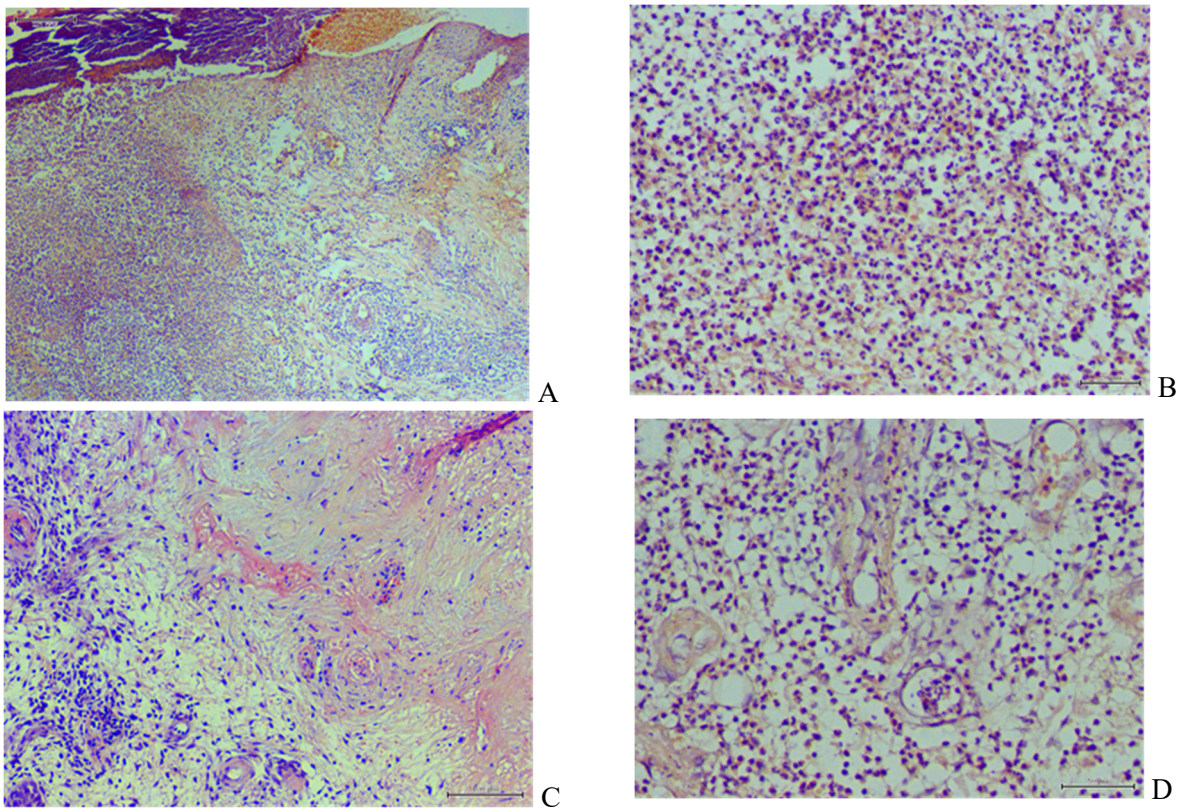

Fig. 2. Pyoderma gangrenosum. A – Abscesses in the dermis. Hematoxylin-eosin, × 40. B – Fragment of an abscess of the dermis with an accumulation of neutrophilic granulocytes. Hematoxylin-eosin, × 200. C – Lymphocytic vasculitis with an outcome in fibrinoid necrosis along the periphery of the abscess. Hematoxylin-eosin, × 100. D – Necrotic vessels with molten walls in the thickness of the abscess. Hematoxylin-eosin, × 200.

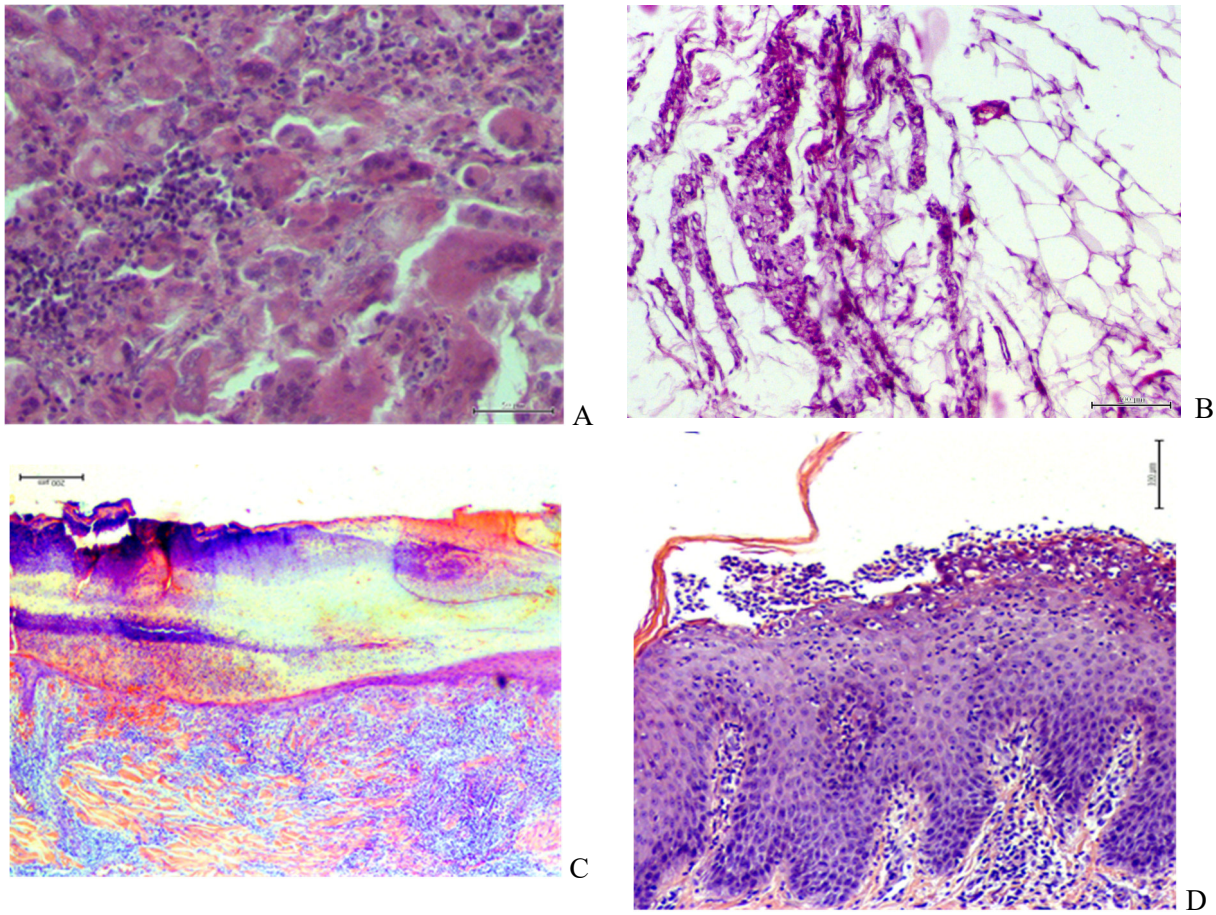

Fig. 3. Pyoderma gangrenosum. A – Giant cells of foreign bodies. Hematoxylin-eosin, × 200. B – Panniculitis development. Hematoxylin-eosin, × 100. C – Bullous form. Hematoxylin-eosin, × 40. D – Subcorneal pustule. Hematoxylin-eosin, × 100.

Based on the presented histomorphological analysis of gangrenous pyoderma, the opinion regarding the specificity of certain forms of this pathology is confirmed. At the same time, the dominant component in all cases of GP is destructive-necrotic and proliferative with the formation of neutrophilic granulomatous cells. It is known that such changes stimulate the accumulation of proinflammatory cytokines (IL-4, IL-13, TNF-α, etc.) in foci of lesions and the activation of endothelial and platelet growth factors. These changes enhance the pathological growth of capillaries, increased bleeding and abnormal reactivity of tissues ("pathergy" phenomenon) [3, 7, 11, 14].

Proper assessment of clinical and histomorphological manifestations in the early stages of GP allows predicting the further course of the disease and choosing the optimal therapeutic algorithm. Thus, ulcerative forms of GP are characterized by the accumulation of necrotic masses with neutrophilic granulocytes, which requires the use of not only systemic corticosteroids, but also local cytostatic complexes with a moderate keratolytic effect.

A massive perfollicular infiltrate, subepidermal edema, and subcorneal pustules characterize morphologically pustular forms of GP. The presence of such morphological changes requires additional use of anti-inflammatory drugs and increased doses of folic acid inhibitors in some cases.

Forms of GP with a hemorrhagic component require special attention when it comes to the inability of the vascular wall to perform its function, which is manifested on the one side by the fragility of microcapillaries and hemorrhages, and on the other by the diapedesis of formed blood elements into the lesions. Figures 2C-2D show signs of vascular damage in the form of panniculitis, while epithelioid cells with the formation of granulomas, which in some cases contained giant cells of foreign bodies, were found in the biopsies of some patients. With such forms of GP, bleeding and tenderness of the elements are possible. When choosing treatment, it is advisable to pay attention to the strengthening of the vascular wall, the possibility of reducing the dose of corticosteroids and cytostatics, topical enzymatic and destructive agents can negatively affect the capacity of the vascular wall and the overall course of the disease.

Separation of the bullous form of GP into a separate form is appropriate because in some cases histomorphological analysis reveals acantholytic cells and intraepidermal cavities, which in the early stages of the disease requires differential diagnosis with autoimmune bullous dermatoses. From a clinical point of view, the topographic zones of lesions in GP differ from pemphigus, but some forms of bullous pemphigoid can manifest themselves in the lower extremities.

The histomorphological picture of the vegetative form of GP is slightly different from the others due to the presence of pseudoepitheliomatous hyperplasia, the formation of sinus passages and microgranulomas against the background of foci of dermal neutrophilic abscesses. The vegetative form is more characterized by the presence of eosinophilic microabscesses in the dermis. The presence of vegetative growths and sinus passages sometimes requires more aggressive topical therapy with local destructive agents. However, it is better to control the effectiveness of GP treatment using intermediate histological studies, the disappearance or reduction of dermal neutrophilic abscesses and eosinophilic microabscesses is a positive sign.

Conclusions

1. Pyoderma gangrenosum is characterized by a variety of clinical forms, a stable protracted course and high comorbidity, all this requires the inclusion of additional research methods in the diagnostic algorithm. When carrying out histological studies of PG, the quality of the biopsy material sampling and the correct interpretation of the results obtained are of great importance. An important pathohistological criterion of PG is pronounced neutrophilic infiltration of all layers of the dermis and epidermis.

2. During the study, specific histological markers were identified for each stage and clinical form of pyoderma gangrenosum. The most significant of them include intravascular fibrin deposition with the subsequent development of fibrinoid necrosis, characteristic of earlier stages of PG, as well as the formation of granulomas containing giant cells of foreign bodies typical of late necrotic stages of PG. Eosinophilic microabscesses were an important histological sign of the vegetative forms of the disease.

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Yu.V. Kyrychenko, L.A. Sarafyniuk, O.V. Androshchuk, O.P. Khapitska, P.V. Sarafyniuk[1]
National Pirogov Memorial Medical University, Vinnytsya
[1]Vinnitsia Mykhailo Kotsyubynskyi State Pedagogical University, Vinnytsya

DETERMINATION OF APPROPRIATE SPIROMETRIC INDICES IN JUVENILE GIRLS OF THE MESOMORPHIC SOMATOTYPE BASED ON MATHEMATICAL MODELING

e-mail: lsarafinyuk@gmail.com

Using multivariate regression analysis, which made it possible to determine the total influence of external structure indicators on the variability of spirographic body parameters, we performed mathematical modelling in girls of the mesomorphic somatotype to determine appropriate individual spirographic indices. For 12 spirometric parameters, linear regression models were built with the accuracy of character description within 55.30–96.64 %. To the greatest extent, the value of spirometric parameters was determined by the body's girth, the pelvis's diameters and the transverse mid-thoracic width of the distal epiphysis.

Key words: spirography, anthropometry, somatotyping, juvenile ontogenesis, regression models.

Ю.В. Кириченко, Л.А. Сарафинюк, О.В. Андрощук, О.П. Хапіцька, П.В. Сарафинюк

ВСТАНОВЛЕННЯ НАЛЕЖНИХ СПІРОМЕТРИЧНИХ ПОКАЗНИКІВ У ДІВЧАТ ЮНАЦЬКОГО ВІКУ МЕЗОМОРФНОГО СОМАТОТИПУ ЗА РАХУНОК МАТЕМАТИЧНОГО МОДЕЛЮВАННЯ

Використавши багатофакторний регресійний аналіз, який дав можливість визначити сумарний вплив показників зовнішньої будови на варіабельність спірографічних параметрів тіла, ми провели математичне моделювання для визначення належних індивідуальних спірографічних показників у практично здорових дівчат юнацького віку мезоморфного соматотипу. Для 12 спірометричних параметрів побудовано регресійні лінійні моделі з точністю опису ознаки у межах 55,30-96,64 %. У найбільшій мірі величина спірометричних параметрів детермінувалася обхватними розмірами тіла, діаметри таза і поперечним середньогрудним, шириною дистальних епіфізів.

Ключові слова: спірографія, антропометрія, соматотипування, юнацький період онтогенезу, регресійні моделі.

The study is a fragment of the research project "Somato-viscometric features of the human body in different periods of ontogenesis", state register No. 0121U113772.

Scientific studies have established a mutually determined relationship between the morpho-functional parameters of various organs and systems and the features of the external structure of the body [5]. It should be noted that a historical excursion into the study of this issue makes it possible to reveal the constitutional features of the morphological and functional indices of the cardiovascular system in various ways [2, 3, 13, 14]. At the same time, the correlations of respiratory indicators with parameters of body