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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии
საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

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GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებში.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman (Кириллица)**, для текста на грузинском языке следует использовать **AcadNusx**. Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи.** Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - <http://www.spinesurgery.ru/files/publish.pdf> и http://www.nlm.nih.gov/bsd/uniform_requirements.html. В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректур авторам не высылаются, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or computer-printed on a single side of standard typing paper, with the left margin of 3 centimeters width, and 1.5 spacing between the lines, typeface - **Times New Roman (Cyrillic)**, print size - 12 (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf

In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

**Articles that Fail to Meet the Aforementioned
Requirements are not Assigned to be Reviewed.**

ავტორთა საყურადღებო!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე, დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx**. შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემავსებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრაფიის ფოტოსურათები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შედეგების ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფხიხლებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

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ASSOCIATION OF PULMONARY AND CUTANEOUS CHANGES IN COVID-19-RELATED CONDITIONS

Gradil G.I¹, Torianyk I.I^{2,3}, Yurko K.V¹, Shiyan D.M⁴, Merkulova N.F¹, Mohylenets O.I¹, Tkachenko V.G¹, Karmazina I.S¹, Lantukh A.P⁵, Hryhorov Y.B⁶, Gargin V.V^{1,4,7}.

¹Kharkiv National Medical University, Kharkiv, Ukraine.

²National Academy of Physical Culture, Kharkiv, Ukraine.

³Private enterprise Polymed, Dnipro, Ukraine.

⁴Private Institution of Higher Education «Kharkiv International Medical University», Kharkiv, Ukraine.

⁵Private Institution of higher education "Kharkiv Institute of Medicine and Biomedical Sciences", Kharkiv, Ukraine.

⁶University of medicine and social sciences, Kharkiv, Ukraine.

⁷Karazin Kharkiv National University, Kharkiv, Ukraine.

Abstract.

Introduction: The study of skin manifestations in COVID-19 is relevant due to the possibility of their appearance before the onset of the typical pattern of respiratory lesions, and the typicality of this pattern has changed noticeably with the emergence of new strains of the virus (nosomorphosis), therefore skin manifestations have both early diagnostic and possible prognostic value.

Aim: The aim of our study was to identify the relationship between the course of SARS-CoV-2 and its specific features of skin manifestations during the COVID-19 pandemic.

Materials and methods: A retrospective study of data from patients with maculopapular lesions who had COVID-19 was conducted. Among all the skin manifestations of COVID, we selected maculopapular lesions for a more detailed study, as one of the most frequent dermatological pathological processes in this disease. Based on the assessment of the area of the lesion and symptoms (the nature of itching, dryness, pain or other accompanying discomfort that interferes with normal activity, sleep; skin peeling), the degree of the course was assessed as mild, moderate, severe. The severe form of the acute respiratory syndrome of the coronavirus 2 (SARS-CoV-2) was diagnosed based on a complex of clinical and laboratory data obtained from the medical histories of persons undergoing examination. Among the clinical and laboratory data, we selected C-reactive protein (CRP - a blood plasma protein belonging to the group of acute phase proteins, the concentration of which increases during inflammation), D-dimer (a protein fragment that is formed during the dissolution of a blood clot that occurs during blood clotting), procalcitonin (a precursor of calcitonin, which is involved in calcium metabolism and maintains its constant level in the blood) and blood oxygen saturation level.

Results: It has been established that moderate and severe SARS-CoV-2 is characterized by skin lesions in the form of maculopapular lesions. Typical are itching, dryness, painful or other accompanying discomfort, skin peeling. In most patients with rash (198 patients (65.8%)) it was a generalized process, more prominent on extremities. Bilateral jawline and periauricular area were affected in 234 (77.7%) patients. In 204 (67.8%) patients, rashes were observed on the abdomen. The average duration of the rash was 10.4±2.21 days.

Conclusions: Among the studied signs, a strong correlation was found between the area of alveolar cell desquamation in the

lungs and such changes as the area of skin lesions, skin peeling ($r=0.73$ and $r=0.74$, respectively), which could be established in deceased individuals. A high dependence of the area of skin lesions on the level of D-dimer ($r=0.71$) and procalcitonin ($r=0.70$) was also found.

Key words. SARS-CoV-2, skin, COVID-19, morphology, nail plate, pathology, maculopapular skin eruptions, desquamation.

Introduction.

Infectious diseases occupy a significant place in the history of mankind, given their prevalence [1-4]. In particular, the SARS-CoV-2/COVID-19 pandemic raises the possibility of the emergence of the next threat, which may be caused by new strains of coronavirus, avian or pandemic influenza. In order to determine how the clinical and morphological features of coronavirus disease are related, a huge number of studies have been conducted in recent years [5,6]. Usually reported on clinicopathological autopsy studies in COVID-19, and indicate that most patients have significant pulmonary pathology, widespread microscopic thromboses, and characteristic findings in the liver and lymph nodes. Most patients showed both exudative and proliferative diffuse alveolar damage [7]. Also often indicate serious endothelial damage in COVID-19, associated with destruction of endothelial cell membranes [8]. In COVID-19, the SARS-CoV-2 virus can cause damage to the lung epithelium, leading to inflammation and destruction of alveolar structures.

Almost from the very beginning of the pandemic, there has been an increase in reports of skin manifestations accompanying infection with the SARS-CoV-2 virus [9], in particular, such as skin angitis caused by SARSCoV-2 itself; papulovesicular rashes; lichen rosacea and papulosquamous rashes; crusted rash; toxicoderma; urticaria; artificial (trophic) changes in facial tissues. Their etiology and pathogenesis cannot yet be considered definitively proven. Dermatological manifestations in COVID-19 may be due to the binding of SARS-CoV-2 to angiotensin-converting enzyme-2 (ACE2) receptors present in skin blood vessels, epithelial cells of endocrine glands, and the basal layer of hair follicles [10]. It is also suggested that these rashes may be caused by a cytokine storm that occurs as a response of an overactive immune system to the virus [9]. Undoubtedly, the possibility of skin manifestations due to adverse reactions to drugs used to treat patients with COVID-19 cannot be ruled out. Finally, American authors in their review

(2024) stated that the mechanisms of the appearance of a rash in COVID-19 have not yet been clearly established [11], while stress related to the COVID-19 pandemic may exacerbate some chronic dermatological diseases [12,13]. The study of skin manifestations in COVID-19 is also relevant due to the possibility of their appearance before the onset of the typical pattern of respiratory lesions, and the typicality of this pattern has changed noticeably with the emergence of new strains of the virus (nosomorphosis), therefore skin manifestations have both early diagnostic and possible prognostic value.

The goal of our work was to identify the relationship between the course of SARS-CoV-2 and its specific features of skin manifestations during the COVID-19 pandemic.

Materials and Methods.

The study was performed in accordance with the principles of the Helsinki Declaration of the World Medical Association "Ethical Principles of Medical Research Concerning Human Subjects" (2013) with written informed consent. A retrospective study of data from patients with maculopapular lesions who had COVID-19 (n=301) was conducted. An analysis of cases due to COVID-19 observed in 2020, 2021, and 2023 at the municipal non-profit enterprise of the Kharkiv Regional Council "Regional Clinical Infectious Diseases Hospital" is presented. Medical records and autopsy protocols (34 deceased) were studied. The diagnosis of COVID-19 in patients was confirmed by PCR with the detection of SARS-CoV-2 RNA, in some patients, JgM and JgG to AG SARS-CoV-2 were detected by immunochromatographic study. An in-depth study of micropreparations of 34 patients who died from COVID-19 was conducted by Professor of the Department of Pathological Anatomy of Kharkiv National Medical University G.I. Gubina-Vakulyk. Average age ($M \pm m$) 61.1 ± 4.5 years deterioration of the condition from the onset of the disease 8.0 ± 2.4 days; bed days on average 6.5 ± 1.3 days; day of illness during hospitalization 9.2 ± 2.4 days; life expectancy 14.8 ± 2.9 days. A more detailed analysis of clinical data is given in our work [14]. To study the morphological state of the lungs, microscopic examination of sections of lung tissue placed on slides stained with hematoxylin and eosin was used [15,16]. With an emphasis on the morphological state of the lungs, pathohistological features of the state of the endothelium of microvessels, hemorrhagic manifestations, thrombus formation, and changes in the interstitial tissue of the lungs were assessed. To obtain digital indicators, the area of desquamation of alveocytes was determined.

Any new cutaneous manifestation not attributable to a previous/pre-existing skin disease or alternative diagnosis was considered COVID-19-related. Among all the skin manifestations of COVID, we selected maculopapular lesions for a more detailed study, as one of the most frequent dermatological pathological processes in this disease [17]. Based on the assessment of the area of the lesion and symptoms (the nature of itching, dryness, pain or other accompanying discomfort that interferes with normal activity, sleep; skin peeling), the degree of the course was assessed as mild, moderate, severe on day of most pronounced changes.

The severe form of the acute respiratory syndrome of the coronavirus 2 (SARS-CoV-2) was diagnosed based on a

complex of clinical and laboratory data [18] obtained from the medical histories of persons undergoing examination on day of admitting in hospital. Among the clinical and laboratory data, we selected C-reactive protein (CRP - a blood plasma protein belonging to the group of acute phase proteins, the concentration of which increases during inflammation), D-dimer (a protein fragment that is formed during the dissolution of a blood clot that occurs during blood clotting), procalcitonin (a precursor of calcitonin, which is involved in calcium metabolism and maintains its constant level in the blood) and blood oxygen saturation level (Table 1). Area of alveocytes desquamation was selected as most important pulmonary findings detected during autopsy [7]. Male and female distribution was equally presented in both groups.

Statistical processing of the data was performed using the Statistica for Windows 8.0 software package. Methods of descriptive statistics (determination of numerical characteristics of variables - arithmetic mean (M), mean sampling error (m), determination of the reliability of differences (p), which were tested via the Student-Fisher t-test in representative samples) were used. Correlation between indicators was assessed using Spearman's correlation coefficient (r). The difference in values between comparative indicators was considered significant at $p < 0.05$.

Results.

Maculopapular-erythematous rashes are characterized by an erythematous skin rash, flat erythematous macules, and/or raised papules. In our study maculopapular lesions (maculopapular rash) was observed as skin rash consisting of a combination of flat spots (macules) and raised bumps (papules) above the skin surface. Majority of patients with maculopapular lesions described that rash began on lower extremities and had spread centrally to her abdomen and upper extremities as non-urticarial, painless, and spared the palms, feet and mucosal surfaces. Indistinct erythematous patches to coalescent maculopapules, some with a violaceous center, in one patient progressed into pustules and desquamation. Mean duration of rash 10.4 ± 2.21 days. In the majority of patients with rash (198 patients (65.8%)) it was generalized process, more prominent on extremities. Bilateral jawline and periauricular area were affected in 234 (77.7%) patients. In 204 (67.8%) patients, rashes were observed on the abdomen. Among those patients who did not die, the rash elements tended to slowly disappear. Moreover, seven maculopapular patterns are identified: morbilliform, other maculopapular eruptions, purpuric, similar to erythema multiforme, pityriasis rosea, as persistent raised erythema, and perifollicular.

Microscopic examination of the lungs revealed the presence of massive thrombosis of blood clots parietally in the absence of vascular endothelium, mainly of the microcirculatory bed. There was mainly serous and hemorrhagic exudate in the alveoli, infiltration of their walls by macrophages in interstitial pneumonia, desquamation of alveolocyttes. The nature of changes in the lungs of those who died from SARS-CoV-2 is shown in Figure 1.

The relationship between indicators of SARS-CoV-2 severity and clinical manifestations of skin lesions is presented in Table 2.

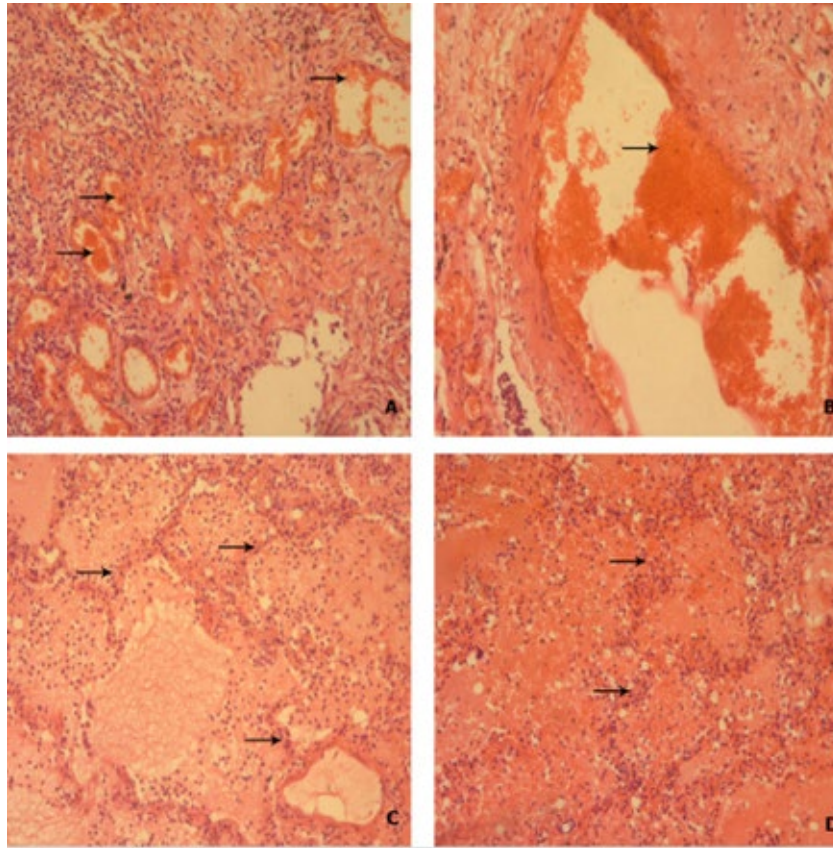


Figure 1. Morphological changes in the lungs of patients with a confirmed diagnosis of COVID-19. *A.* Several thrombi in the pulmonary vessels, including the parietal one (indicated by the arrow), complete absence of endothelium. Hematoxylin and eosin staining, magnification x200. *B.* Parietal thrombus growing into the lumen of the pulmonary vessel with the possibility of obstruction. Hematoxylin and eosin staining, magnification x200. *C.* Interstitial pneumonia. Serous and hemorrhagic exudate in the alveoli, infiltration of their walls by macrophages. Hematoxylin and eosin staining, magnification x200. *D.* Interstitial pneumonia, macrophages and lymphocytes in the alveolar walls (indicated by the arrows). Hematoxylin and eosin staining, magnification x200.

Table 1. Laboratory and microscopic findings in the COVID-19 patients.

Parameters and their values	
C-reactive protein, mg/l	98.63±9.17
D-dimer, ng/ml	769±32.82
Procalcitonin, ng/ml	0.64±0.13
Blood oxygen saturation level (%)	85.17±5.77
Area of desquamation of alveocytes (%)	74.13±7.02

Table 2. Relationship between SARS-CoV-2 severity indicators and clinical manifestations of skin lesions (*r*).

Severity index of SARS-CoV-2	Area of skin lesions	Severity of itching	Dry skin	Pain or other discomfort	Skin peeling
C-reactive protein	0.49	0.38	0.40	0.43	0.54
D-dimer	0.71	0.53	0.38	0.58	0.49
Procalcitonin	0.70	0.53	0.51	0.41	0.43
Oxygen saturation	0.36	0.47	0.67	0.51	0.45
Area of desquamation of alveocytes	0.73	0.63	0.66	0.64	0.74

Discussion.

Modern medicine is characterised by collaboration of specialists from variable fields [19-21]. The high level of contagiousness and asymptomatic transmission of the infection led to its rapid spread around the world and the development of a pandemic. Not only infectious disease specialists, but also general practitioners, outpatient clinics, anesthesiologists, intensive care physicians, neurologists, and dermatologists are faced with coronavirus infection. Skin manifestations of COVID-19 occur in approximately 20% of patients and sometimes appear before classic symptoms (cough, fever). They are caused by the immune system's response to the virus or microcirculation disorders, are most often self-limiting, and require mainly symptomatic treatment. Our study showed that patients with confirmed COVID-19 could display various cutaneous manifestations [22]. Maculopapular lesions (maculopapular rash) is a skin rash consisting of a combination of flat spots (macules) and raised bumps (papules) above the skin surface. It is not a separate diagnosis, but a symptom that can be a common skin manifestation of infection, mainly in adults. The hypothetical cause of the maculopapular rash could be a cytokine storm of the hyperinflammatory phase. It is generally accepted that such a rash could be an adverse reaction of the body to the drugs used to treat COVID-19, however, in some patients who were not treated pharmacologically, a maculopapular rash was found [23]. Vesicular "pox-like" lesions appeared predominantly on the trunk as monomorphic vesicles, occasionally with hemorrhagic contents, on an erythematous base, and resembled chickenpox. A potential pathophysiological mechanism for the appearance of vesicular lesions is a cytokine storm, which is the result of excessive reactivity of the immune system or direct effects of the coronavirus on the vascular endothelium [23,24]. It is suggested that the "morbilloform" erythematous lesions and skin lesions resembling erythema multiforme may not have been caused directly by SARS-CoV-2 infection.

Hyperactive immune responses in COVID-19 patients may contribute to the induction of a cytokine storm (particularly mediated by interleukin-6); these cytokines can infiltrate the skin, particularly dermal dendritic cells, lymphocytes, macrophages, mast cells, and neutrophils, and may contribute to the development of lesions such as maculopapular rash. This pattern of skin lesions has been previously described in diseases associated with hyperactive immune responses and excessive cytokine release (including systemic lupus erythematosus, adult-onset Still's disease, and antiphospholipid syndrome) [25]; cutaneous manifestations may be an early sign of immunological reactions in other parts of the body, similar to pulmonary infiltrates resulting from a cytokine storm.

From a histological point of view, several features of the maculopapular skin lesion in COVID-19 have been identified. Histological examination of the maculopapular lesions shows superficial perivascular dermatitis with lymphocytic infiltrate and dilated vessels in the papillary and mid-dermis with neutrophils, eosinophils and nuclear fragments. The epidermis shows scattered foci of hydropic changes accompanied by minimal acanthosis, subcorneal pustules, slight spongiosis, basal cell vacuolization, and foci of parakeratosis [17]. Similar

changes could be observed in other pathological processes also [26]. But it should be recognised with the detailing of pathogenetic links for adequate treatment [27-29].

A feature of our work was the identification of a possible relationship between the signs of the severity of the course SARS-CoV-2 and skin rashes. Among the studies conducted, a strong correlation between the area of alveolar cell desquamation in the lungs and changes such as the area of skin lesions, skin peeling ($r=0.73$ and $r=0.74$ respectively), which could be established in deceased individuals. Also, a high dependence of the area of skin lesions on the level of D-dimer was found ($r=0.71$) and procalcitonin ($r=0.70$). Exactly detected correlations prove that described skin lesions are result of SARS-CoV-2 but not comorbidities, medication effects, and post-COVID conditions.

The above gives reason to assume that the mechanisms underlying desquamation in the lungs and skin lesions have similar links in pathogenesis, since the sequence of changes in the lungs and skin does not seem obvious.

A maculo-papular rash appears concomitantly with the other symptoms of infection and lasts for a short period (3–10 days), and itching is reported in most of the patients. It is often associated with severe disease in older patients [30]. Usually it's reported a prevalence of half patients. There is description of bed a perifollicular distribution in some cases and occasionally scaling. The erythematous rash may be particularly accentuated on the antecubital fossa and axillary folds. Skin biopsy shows some non-specific features of viral-related exanthema, such as slight spongiosis and mild perivascular lymphocytic infiltrate [30-32].

Potential reasons for this could be microthrombi formed due to activation of the complement system by immunoglobulins, increased concentrations of D-dimers and fibrin degradation products in the serum of patients with COVID-19, and prolonged prothrombin time.

There is a need to further diagnose the cutaneous manifestations of SARS-CoV-2 infection and to learn the detailed pathomechanism of their occurrence in order to better understand the essence of the disease and find an appropriate treatment method [12]. Using of digital medicine achievement should be implemented as way for obtaining faster diagnosis [33,34].

The study of skin manifestations of SARS-CoV-2 infection is important for the rapid identification of new patterns associated with the evolution of the virus, the adaptation of medical approaches to treatment and prevention, and is an important component of an effective strategy for responding to and preparing for pandemics [35,36]. The involvement of dermatovenereologists plays an important role in the response to the COVID-19 pandemic due to the possibility of early diagnosis of skin lesions indicative of SARS-CoV-2 infection, especially in asymptomatic cases, which will certainly contribute to improving the prognosis of the disease. Skin manifestations are significant for diagnosis, but they are difficult to recognize due to the impossibility of conducting routine dermatological consultations of such patients during the pandemic. Physicians' awareness of skin symptoms associated with COVID-19 infection is crucial to prevent misdiagnosis, as well as for the timely appointment of adequate treatment.

The skin, including mucous membranes, is an organ that frequently presents lesions caused by viral infections (e.g., dengue, Zika, measles, chickenpox, herpes zoster among others). These infections may be primarily localized in the skin or manifest at the cutaneous-mucosal level as part of the general symptomatology [37]. And maculopapular rashes could be pathophysiologically explained in SARS-CoV-2 by development of cytokine storm,

direct cytopathic effect of the moderate course SARS-CoV-2. The oral antihistamines, topical corticosteroids, systemic corticosteroids in more severe or generalized affections could be recommended for treatment [37].

Conclusion.

The maculopapular lesions is common manifestation of moderate and severe course of SARS-CoV-2. Typical are itching, dryness, painful or other accompanying discomfort, skin peeling. In most patients with rash (198 patients (65.8%)) it was a generalized process, more prominent on extremities. Bilateral jawline and periauricular area were affected in 234 (77.7%) patients. In 204 (67.8%) patients, rashes were observed on the abdomen. The average duration of the rash was 10.4 ± 2.21 days. Among the studied signs, a strong correlation was found between the area of alveolar cell desquamation in the lungs and such changes as the area of skin lesions, skin peeling ($r=0.73$ and $r=0.74$, respectively), which could be established in deceased individuals. A high dependence of the area of skin lesions on the level of D-dimer ($r=0.71$) and procalcitonin ($r=0.70$) was also found.

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Conflict of interest statement.

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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