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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 ВИНИТИ 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 ВИНИТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

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. Корректура авторам не высылается, 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 compu-ter-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 საყურადღებოდ!

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, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის 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 ფჩხილებში 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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SYMPTOMATOLOGY AND TREATMENT OF COVID-19 AFFECTING SKIN APPENDAGES: A NARRATIVE REVIEW BEYOND COVID-TOES

Uwe Wollina[1]*, Ayman Abdelmaksoud[2,3], Anca Chiriac[4,5], Piotr Brzezinski[6,7], Selami Aykut Temiz[8].

[1]*Department of Dermatology and Allergology, Städtisches Klinikum Dresden, Academic Teaching Hospital, 01067 Dresden, Germany.*

[2]*Mansoura Dermatology, Venerology and Leprology Hospital, Mansoura, Egypt.*

[3]*Department of Dermatology, University of Studies Guglielmo Marconi, Rome, Italy.*

[4]*Nicolina Medical Center, Department of Dermatology, Apollonia University, Iași, Romania*

[5]*"Petru Poni"" Institute of Macromolecular Chemistry, Romanian Academy, Iași, Romania.*

[6]*Department of Physiotherapy and Medical Emergency, Faculty of Health Sciences, Pomeranian Academy, Slupsk, Poland.*

[7]*Department of Dermatology Voivodship Specialist Hospital in Slupsk, Ustka, Poland.*

[8]*Department of Dermatology, Necmettin Erbakan University Meram Medical Faculty, Konya, Turkey.*

Abstract.

Background: SARS-CoV-2 is the cause of COVID-19 disease and responsible for a pandemic since the 2020. Multiple organ involvement has been described including cutaneous symptoms. Affection of skin appendages, however, seems to be under-reported except for COVID-toes.

Material and methods: We performed a PUBMED research for "COVID-19" OR "SARS-CoV-2" AND "skin appendages", "hair", "nails", and "skin glands" from January 2020 to April 2022. COVID toes were excluded since this symptom had extensively been discussed. The focus of this narrative review was laid on clinical presentation, association to the course of COVID-19 disease and treatment options.

Results: Skin appendages can be affected by COVID-19 disease beyond COVID-toes, both by symptomatic and asymptomatic course. Telogen effluvium, androgenetic alopecia, and alopecia areata are the most common hair disorders in COVID-19 patients. Nails are less commonly affected by COVID-19 than hair. Splinter hemorrhages and leukonychia are the most frequent findings. While sebaceous glands seem to be uninvolved, SARS-CoV-2 spike proteins have been identified in eccrine sweat glands.

Alopecia areata is often seen among asymptomatic COVID-19 patients while telogen effluvium is observed in symptomatic and asymptomatic patients. The half-moon sign on the nails could be a red flag for a more severe course of COVID-19. Treatment options are summarized.

Conclusions: Skin appendages are not spared by COVID-19. Their knowledge will help to identify asymptomatic patients and patients at risk for a more severe course of the viral disease.

Key words. COVID-19, SARS-CoV-2, hair, nails, skin glands, treatment.

Introduction.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an RNA beta-corona virus of group IIb, responsible for coronavirus disease 19 (COVID-19). The virus consists of four structural proteins, i.e., spike, membrane, envelope, and nucleocapsid proteins, and encodes for another 25 non-structural proteins [1]. Transmission is mainly by droplets. The angiotensin-converting enzyme 2 (ACE2) receptor is a critical structure for viral entry into human cells. ACE 2 receptors have been detected on various cells including keratinocytes and cutaneous endothelial cells [2,3]. Transmembrane protease serine 2 (TMPRRS2) receptor is another important host cell-entry modulator [4]. The androgen receptor regulates the transcription of TMPRSS2 [5].

The origin of COVID-19 was Wuhan, China, but the disease has spread rapidly and has become a pandemic since 2020. Pneumonia and hypogeusia/hyposmia were the leading symptoms during the first wave [6,7]. Cutaneous symptoms had been under-reported in the early period, but at least during the first wave in Northern Italy, cutaneous symptoms have become more and more recognized and became classified into diagnostically and prognostically important clinical symptoms [8-10]. The affections of skin appendages like hair, nails, and skin glands are lesser known.

This review will focus on manifestations of COVID-19 in cutaneous appendages, clinical features, and treatment.

Material and methods.

PUBMED database was screened for "COVID-19" OR "SARS-CoV-2" AND "Hair", "Nails", "Skin glands" from 2019 to April 2022. In addition, three papers of hand research were considered. We focused on clinical manifestations, relationship to clinical course of COVID-19, and treatment of skin appendage manifestations during or post COVID-19 disease. We detected 853 papers on cutaneous manifestations of COVID-19. Articles on cutaneous symptoms in COVID-19 disease without mentioning skin appendage manifestations in detail were excluded. Seventy-one articles included detailed mentioning of skin appendage manifestations. Three of them were excluded due to limited quality. Eventually, 68 papers have been considered in this narrative review. For treatment options, some other relevant publications were added.

Hair.

Androgenetic alopecia (AGA) is triggered by sexual hormones and has characteristic though different patterns of hair loss among males and females. In a current review including 1826 patients with alopecia and COVID-19, AGA was the most common type of alopecia observed in 30.7% of patients with 86.4% males. AGA was commonly pre-existent but worsened during and after COVID-19 [11].

Hair loss in COVID-19 patients has been observed in about 20% - 66% post-COVID [12-15]. This hair loss is consistent with telogen effluvium characterized by sudden, non-scarring

hair loss 2–3 months after the causal event. The percentage of telogen hair is diminished to 20% or less. Trichoscopy showed regrowing hairs, follicular units with single hair, empty hair follicles, and thin terminal hairs – findings that are typically for telogen effluvium. In a meta-analysis of published studies, 465 were identified with acute telogen effluvium that developed on average 74 days after COVID-19 symptoms appeared. Two-third of patients were females, the median age was 44 years [16]. A possible link between severity of COVID-19 disease and severity of hair loss, hair greying, and scalp allodynia is debatable [17,18].

Of interest, Wambier and Tosti (2022) reported that 8 out of 25 patients with post-COVID–19 TE had patchy body hair effluvium, even without scalp patchy alopecia [19]. Aksoy et al. (2021) observed that post-COVID-19 TE was more frequent in hospitalized female patients with hypertension, who had respiratory symptoms, representing 27.9% of their cohort [20].

Characteristic for TE are the following findings: positive pull test result, some empty follicles in trichoscopy, and >20% telogen hairs in trichogramm. Histologically, there is no relevant miniaturization and no inflammatory reaction in the epidermis or hair follicles [21].

Guarneri et al. (2022) investigated 104 patients with COVID-19 pneumonia. Looking for hospitalized patients who had a more severe disease, 18% of men and 60% of females complained about hair loss. Medication with either methylprednisolone, enoxaparin or hydro chloroquine increased the Odd's ratio to 15.77, while smoking had an Odd's ratio of 2.12 [22]. A possible explanation is the release of multiple cytokines (cytokine storm) such as interleukin (IL)-1 beta, IL-6, interferon gamma, and tumor necrosis factor alpha but this was not substantiated by histological findings [21,23].

Some disorders bear a higher risk of hair loss after SARS-CoV-2 infection. One trial analyzed 56 households with patients suffering from hypohidrotic ectodermal dysplasia (HED). Hair loss was significantly more common among HED patients (64%) than in the control group (13%) [24].

Regrowth of hair can be expected in most patients with TE [25]. Despite being a self-limiting condition, hair loss post-COVID-19 is a stressful event.

The following treatments have been used for TE among COVID-19 patients: 2% and 5% topical minoxidil, oral minoxidil, oral nutricosmetics, platelet-rich plasma (PRP) injections among others (Table 1) [26].

Piebaldism and Wardenberg syndrome may present with a white forelock among other hypopigmented lesions. There is one report from Italy about repigmentation of the hair in a 3-month-year-old baby girl after COVID-19 [27].

Alopecia areata (AA) is a common kind of autoimmune non-scarring hair loss, which can occur recurrently. Pre-existent AA may be worsened or relapsed by COVID-19 [28]. In general AA has less often been reported in COVID-19 patients [29-32]. AA counts for 7.8% of alopecia cases with a female predominance [11]. Fortunately, AA totalis is a rare event [33]. TE and AA can also affect children with COVID-19-related multisystem inflammatory syndrome [34]. The relapse rate of AA was significantly higher in COVID-19 patients versus non-COVID patients in an Italian study [35].

There are three major mechanisms that are discussed for AA: (a) the increased stress level during the pandemic, especially during lockdown, (b) the cytokine storm by SARS-CoV-2 infection, and (c) a possible cross-reaction of the viral antigen with self-antigens of the dermal papilla [36,37]. It has been suggested that monocytes infected by SARS-CoV-2 may play a fundamental role in the development of post-COVID-19 TE [38]. Ma et al. (2022) reported that SARS-CoV-2 could mostly target the KRT17+ hair follicle cells ex vivo [39]. Furthermore, oxidative stress can lead to increased liberation of tumor necrosis factor alpha and interferon gamma, interfering with T cell activation [40].

During the acute infection anagen effluvium has rarely been described in COVID-19 patients [41,42].

Trichodynia – the painful hair or scalp dysesthesia syndrome – is a symptom that often but not exclusively can be associated

Table 1. *Treatment of COVID-19 associated hair disorders.*

Disorder	**Treatment options**	**References**
Anagen effluvium	Topical minoxidil (limited efficacy)	Saleh et al. 2022
Androgenetic alopecia	Topical minoxidil 2% (females)	Kelly et al. 2016
	Topical minoxidil 5% (males)	
	Oral finasteride 1 mg/d (males)	
	Oral 2 mg cyproteronacetate + 35 µg ethinylestradiol (females)	
Alopecia areata	Intralesional, topical or systemic corticosteroids	Sterkens et al. 2021
	Oral corticosteroid pulse therapy	Sánchez-Díaz et al. 2022
	Topical dinitrochlorobenzene, diphenylcyclopropenone,	Sterkens et al. 2021
	squaric acid dibutylester (contact sensitization)	Georgescu et al. 2022
	Platelet-rich plasma	Petrov & Vasileva 2021
	Janus kinase inhibitor (under investigation)	Zheng & Tosti 2022
Telogen effluvium	Topical corticosteroids (for acute and chronic type)	Asghar et al. 2020
	Oral corticosteroids (for chronic type)	
	Peptide mimicking hair growth factor lotion	Rizetti et al. 2021
	QR678 Neo® hair growth factor formulation	Shome et al. 2022
Trichodynia	Topical corticosteroids	Kelly et al. 2016
	Oral propranolol 10 mg/d	Brzezinski et al. 2019

with TE. It does not show an association to the severity of hair loss either. Among COVID-19 patients, trichodynia has been reported in 42.4% of COVID-19 cases [14].

Temporary yellow-green fluorescence has been observed in hair of faripiravir treated patients under Wood's light. There is no clear association between total dosage of the drug and intensity of fluorescence [43]. One study mentioned a decrease of fluorescence after 58 days [44]. Clinical examples of hair disorders due to COVID-19 are shown in Figures 1 and 2. Treatment of hair disorders caused by COVID-19 is summarized in Table 1 [41-54].

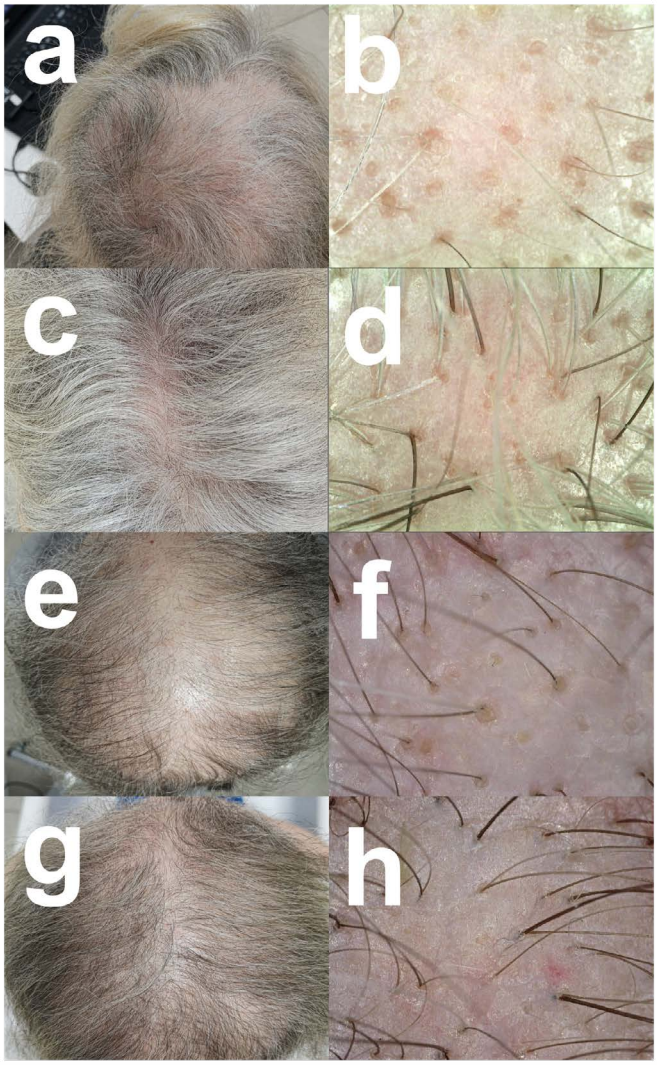

Figure.1. *Telogen effluvium in COVID-19 patients. Clinical presentation and trichoscopy. (a) - (b) 51-year-old woman, (c) – (d) 56-year-old woman. In both patients, excessive hair appeared 2 months after the first symptoms of SARS-CoV-2 infection and lasted for about 3 months. Gray hair dominated in the areas of greatest thinning. These patients were not hospitalized during their COVID-19 disease. (e) - (f) 60-year-old woman and (g) - (h) 58-year-old woman – both with a moderate SARS-CoV-2 infection. Telogen effluvium developed about 1.5 months after confirmed infection and lasted for about 2 months.*

Figure. 2. *Alopecia areata in COVID-19 patients. (a) A 9-year-old asymptomatic girl. (b) A 6-year-old asymptomatic girl. (c) Another 6-year-old asymptomatic girl. (d) A 13-year-old asymptomatic boy with a mottled appearance of hair loss. (e) A 30-year-old woman, who was hospitalized and needed assisted ventilation for 6 days.*

Nails.

Nail changes have long been under-reported in COVID-19 patients [55]. In a study from Turkey, 174 COVID-19 patients were screened for nail symptoms. The most common nail findings were splinter hemorrhage (13%), leukonychia (12%), and longitudinal ridges (7.9%) [56].

Recent reviews summarized published data on nail changes in COVID-19 patients. They authors identified red half-moon nail sign, transverse orange nail lesions, Mees' lines, and Beau's lines [57,58]. Among 93 COVID-19 patients from Bangkok, only 2 reported nail disease, i.e., chromonychia and brittle nails. These patients had a mild COVID-19 disease [59].

A 60-year-old woman, who had COVID-19, presented 2 weeks after symptoms onset, with a distally convex half-moon-shaped red band surrounding the distal margin of the lunula. This band appeared on all fingernails. It was coined red half-moon nail sign by Neri et al. [60]. Microvascular changes and microthrombi seem to be involved. The sign is a red flag for a more severe course of COVID-19 [61,62]. Ocampo-Garza et al. (2021) noted that red half-moon nail sign can be observed between 2 and 14 days after COVID-19 diagnosis in contrast

to distal orange discoloration which develops post COVID. Intriguingly, three patients with red half-moon nail sign were hospitalized and one warranted oxygen requirements [63].

Some pediatric and adult patients presented with horizontal groove over all fingernails and toenails about 3 weeks to 3 months after confirmed COVID-19 disease. These grooves, known as Beau's lines, are often seen after toxic or infectious transient interruption of the proximal nail matrix growth [64-67].

Half and half nails (Lindsay's nails) are characterized as a nail with a white proximal portion and a reddish-brown or a pink distal portion, with a sharp demarcation line between the two. Often seen among patients with chronic renal disease, half and half nails may also occur during COVID-19 disease [68].

Karahan et al. (2022) investigated COVID-19 pneumonia patients admitted to an ICU unit in Turkey using nailfold video-capillaroscopy. Capillary findings were more pronounced in patients with a fatal course compared to survivors. Commonly observed serpentine capillaries had an increased loop diameter compared to non-COVID patients, while the mean capillary density decreased. Other significant findings in COVID-19 patients were giant capillaries, avascular areas, micro-aneurysms, and micro-hemorrhages [69].

Leukonychia and onychomadesis are other possible manifestations of SARS-CoV-2 infection on the nail apparatus. Combined retronychia, onychomadesis and red half-moon sign have been reported in a 59-year-old woman twelve weeks after PCR-confirmed SARS-CoV-2 infection [70].

Nail plate discolorations have also been observed - sometimes due to medications [55,71]. Bright white or yellow green fluorescence of nails under Wood's light has been ascribed to favipiravir [43,72]. Tammaro et al. (2021) reported an 89-year-old woman who developed orange discolorations at the end of her fingers nail beds 16-week post-COVID19 exposure (post-COVID-19 syndrome) [73]. Demir et al. (2021) reported 23-year-old male patient with past history of COVID-19, who presented with heterogeneous red-white discoloration and distal onycholytic areas of all nails (Terry's nails) [74]. Red nail bands associated with TE are a possible post-COVID-19 phenomenon [75].

Clinical examples are shown in Figure 3. Treatment options are summarized in Table 2 [55,62,66,67,76,77].

Eccrine glands.

The first description of SARS-CoV-2 infection of eccrine sweat ducts and glands - in particularly of Krt7+ luminal cells – came from China [78].

An Italian study analyzed 10 children with papulo-purpuric lesions, 3 of them were tested positive for SARS-CoV-2. Immunohistochemistry with a SARS-CoV-2 (2019-nCoV) nucleocapsid antibody resulted in a cuticular staining pattern of the deep portion of eccrine sweat glands [79]. A 35-year-old woman with COVID-19 presented purpuric cutaneous lesions. Immunohistochemistry for SARS-CoV-2 spike protein detected fine to coarse, bright red granular deposits in the cytoplasm of eccrine secretory and excretory cells [80]. In two patients presenting with urticarial vasculitis, nucleocapsid staining of eccrine glands was demonstrated in either reticula dermis or subcutaneous adipose tissue [81].

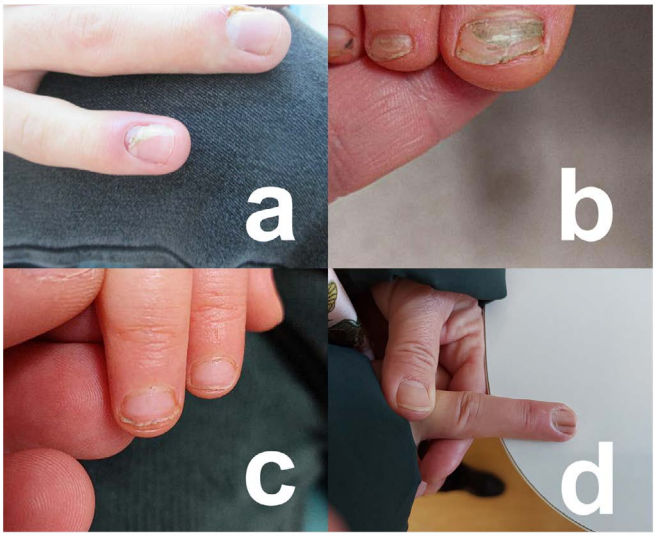

Figure. 3. *Nail disorders in COVID-19 patients. (a) Beau's line on the V. finger post-COVID, (b) Beau's line on the great toenail in a 2-year-old girl with asymptomatic Omicron variant. (c) Onychoschisis (brittle nails) in a 3-year-old boy with asymptomatic Omicron variant. (d) Acquired longitudinal melanonychia post-COVID in a child.*

Table 2. *Treatment options in COVID-19 associated nail disorders.*

Disorder/ Symptom	**Treatment options**	**References**
Beau's line	Self-limited, no treatment necessary	Khemani & Khubchandani 2007
Onychomadesis	Self-limited, no treatment necessary	Salgado et al. 2017
Discoloration of the nail plate	No specific treatment available, exclude mycosis	Wollina et al. 2021
Periungual desquamation	Moisturizers	Wollina et al. 2021
Splinter hemorrhages	No specific treatment available	Wollina et al. 2021
Half-moon sign	No specific treatment available	Farajzadeh et al. 2021
Half-and-half nails	No specific treatment available	Kunimoto et al. 2021
Brittle nails	Biotin 10 mg/d for 3-6 months	Chessa et al. 2020

An 89-year-old man presented with COVID-19 related skin rash. Immunohistochemistry for SARS-CoV-2 spike protein showed positive perinuclear staining in secretory cells of eccrine glands, inner cells of dermal ducts, and acrosyringia [82]. Immunohistochemical findings are further supported by the detection of virions in the cytoplasm of eccrine epithelial cells [83].

The presence of the virus in eccrine glands suggests sweat as a source of contagion, but more studies are needed [84,85]. There is no specific treatment available.

Sebaceous glands.

No direct affection of sebaceous glands has yet been observed. In a single case of COVID-19 with Stevens-Johnson syndrome

(SJS) destruction of Meibomian glands had been reported [86]. SJS seemed to be responsible rather than COVID-19.

Conclusions.

Although skin appendages have not been described as primarily affected by SARS Cov2 infection, due to increasing reports published during the last two years, various manifestations have been described. It is not clear if these manifestations occur as direct effects of infection, inflammatory cytokines in the cutaneous millieu or adverse drug reactions due to medications used by patients. There is a debate on any correlation between them and onset or severity of COVID-19 disease. Some findings may just coincidental. Treatment of COVID-19 seems not to interfere with the evolution of skin appendage disorders in the great majority of cases, except the finding of favipiravir induced fluorescence of keratinous material.

For daily practice skin appendage manifestations related to COVID 19 enrich the long list of comorbidities in SARS-Cov2 infection.

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Conflicts of interest.

U. Wollina, A. Abdelmaksouk, A. Chiriac, P. Brezezinski, and S. Aykut Temiz declare that they have no competing interests.

ORCID.

Uwe Wollina https://orcid.org/0000-0001-5933-2913

Ayman Abdelmaksouk https://orcid.org/0000-0003-4848-959X

Piotr Brzezinski https://orcid.org/0000-0001-6817-606X

Selami Aykut Temiz http://orcid.org/0000-0003-4878-0045

Photo consent statement.

Permission was obtained for publishing clinical pictures by patients or the parents, as appropriate.

Statement of contribution.

The concept had been developed by UW and AA. Material sampling was done by AA, AC, PB, SAT and UW. AA, AC, PB, SAT and UW contributed to the final manuscript. All authors have read and confirmed the final manuscript.

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