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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 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. 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 საქურაღებოლ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დაიცვათ 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, ანათალებების 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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POST-COVID-19 INFLAMMATORY RHEUMATOID ARTHRITIS REMISSION

Takuma Hayashi^{1,2*}, Ikuo Konishi^{1,2,3}

¹Cancer Medicine, National Hospital Organization Kyoto Medical Center, Kyoto-city, Kyoto 612-8555, Japan.

²Medical R&D Promotion Project, The Japan Agency for Medical Research and Development (AMED), Chuo-ku, Tokyo 103-0022, Japan.

³Kyoto University School of Medicine, Kyoto-city, Kyoto 606-8507, Japan.

Abstract.

People infected with the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) are at a higher risk of developing autoimmune inflammatory rheumatic disease. However, clinical studies have shown that, unlike bacterial infections, inflammatory rheumatoid arthritis is rarely triggered by viral infections. Generally, adult females have a higher incidence of rheumatoid arthritis compared to males (a female/male ratio of approximately 3:1). The secretion of female hormones is presumed to be deeply involved in the onset of rheumatoid arthritis. Furthermore, there is a definitive role of genetic factors in rheumatoid arthritis. Typically, rheumatoid arthritis is treated with steroids and antibody drugs, such as anti-tumor necrosis factor- α (TNF- α) antibodies and anti-interleukin-6 (IL-6) antibodies; however, although the symptoms of autoimmune diseases are alleviated by these drugs, the underlying pathology cannot be completely cured. Meanwhile, immunosuppressive treatment with steroids is effective against inflammatory rheumatoid arthritis associated with coronavirus disease (COVID-19). Therefore, the pathogenesis, symptoms, and pathological findings of inflammatory rheumatoid arthritis associated with COVID-19 are presumably different from those of autoimmune rheumatoid arthritis. Since COVID-19-related autoimmune-like diseases, such as COVID-19-related inflammatory rheumatoid arthritis, have pathological conditions that are different from inherited autoimmune diseases, it is possible to establish treatments that aim at remission. Further pathological analyses of patients with post-COVID-19 inflammatory rheumatoid arthritis are essential to the development of treatments for this type of arthritis.

Key words. COVID-19, rheumatoid arthritis, interleukin 6, SARS-CoV-2.

The coronavirus disease-2019 (COVID-19) pandemic was caused by infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Ever since the outbreak in December 2019, the number of confirmed cases of COVID-19 reached 774 million in January 2024, with approximately 7 million deaths worldwide [1]. Clinically, the SARS-CoV-2 infection can present with varying symptoms [2], and any COVID-19 symptoms generally resolve within 2–4 weeks. However, some persons experience long-term sequelae of the disease, which is often referred to as “long COVID” or “post-acute COVID-19 syndrome” [3–5]. As per a nationwide study conducted clinical institution in United Kingdom (UK), approximately 12.8% of participants (matched by age, sex, and socioeconomic status) showed residual COVID-19 symptoms at 12 months after SARS-CoV-2 infection [6]. Furthermore, data from recent clinical research demonstrates a higher risk for

autoimmune inflammatory rheumatic diseases (AIRDs) among patients with a history of COVID-19 [7–9].

It is well-known that SARS-CoV-2 infection is a potential trigger for the development of inflammatory arthritis, not only in people with a history of inflammatory rheumatic diseases but also in those without any such medical history. However, the diagnosis of inflammatory arthritis is complex because new-onset inflammatory arthritis after COVID-19 infection is a heterogeneous phenomenon. For instance, acute arthritis with features of viral arthritis developing after a COVID-19 infection is similar to crystal-induced arthritis. Likewise, there are also reports of post-COVID-19 arthritis mimicking reactive arthritis (ReA); however, the typical features of ReA are often absent in patients who develop this type of arthritis. Furthermore, some studies have reported first-onset cases of inflammatory arthritis in peoples older than 45 years; however, in many of these cases, the Human Leukocyte Antigen (HLA)-B27, which is a genetic characteristic of ReA, was hardly detected. Similarly, rheumatoid factor (RF) has also never been detected in the serum of patients with post-COVID-19 arthritis.

Typically, viral infections are much less likely to cause ReA than bacterial infections. In most patients with post-COVID-19 arthritis, microscopy, culture, and polymerase chain reaction tests for bacterial infection were all negative. Therefore, it is still unclear whether SARS-CoV-2 causes true ReA because viral infection-triggered respiratory illnesses rarely cause ReA. A Korean hospital-based study by Kim et al. [10] reported that SARS-CoV-2 infection was associated with an increased risk of AIRD compared with matched patients without SARS-CoV-2 infection or with influenza infection. Additionally, the risk of AIRD was higher with greater severity of acute COVID-19 [10].

Rheumatoid arthritis is an autoimmune disease that is more likely to occur in women. In Japan, the reported male-to-female incidence ratio of rheumatoid arthritis is 1:4 [11]. Notably, the incidence rate of all autoimmune diseases in Japan is higher in females than males. The most plausible explanation for this higher incidence of autoimmune diseases in females is the role of female sex hormones [12]. However, female hormones do not directly cause disease; instead, they are more likely to activate autoantibodies and cytokines that promote immune responses [13].

A clinical study conducted in Japan reported that compared to non-infected individuals, females had a higher risk of developing rheumatoid arthritis after a COVID-19 infection (odds ratio [OR]: females: 3.04 (95% confidence interval [CI]: 2.81–3.34); males = 2.62 (95% CI: 2.26–3.04)), i.e., females had a 1.172-times higher risk of developing rheumatoid arthritis than males after contracting a COVID-19 infection [14]. Notably, the

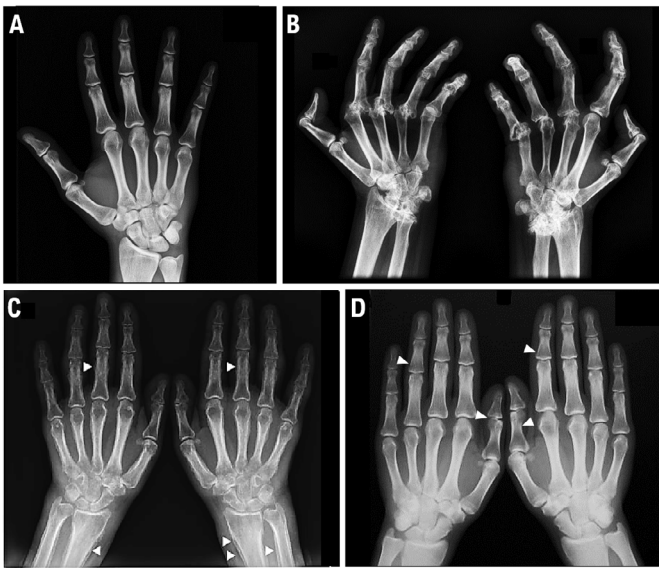


Figure 1. Unlike autoimmune rheumatoid arthritis, the inflammatory rheumatoid arthritis associated with coronavirus disease 2019 (COVID-19) does not cause joint-level deformities due to cartilage and ligament damage.

A. X-ray image of a normal hand with healthy bones and joints derived from a healthy person. **B.** X-ray image of an advanced case of rheumatoid arthritis showing dislocation and destruction of the joints. In rheumatoid arthritis, the cartilage and ligaments supporting the joints are damaged due to autoimmune action, resulting in obvious deformities. **C.** Rheumatic syndromes associated with immune checkpoint inhibitors therapy representative image of periostitis in a patient developing hypertrophic osteoarthropathy after treatment with immune checkpoint inhibitors (white triangles indicate inflammatory findings in the joints). **D.** Rheumatic syndrome in a patient who developed COVID-19 infection. White triangles indicate inflammatory findings in the joints; however, the radiograph of the left hand shows no bony lesions. The authors received informed consent from each patient, and these X-ray images are included in the manuscript.

histopathological and radiographic findings observed in many women with inflammatory rheumatoid arthritis after COVID-19 infection are different from those typically seen in rheumatoid arthritis as an autoimmune disease (Figures 1A, B, and D).

Autoimmune-like diseases are often seen as side effects or immune-related Adverse Events (irAEs) due to the administration of immune checkpoint inhibitors (ICIs) prescribed for cancer treatment. Radiographs of patients with post-COVID inflammatory rheumatoid arthritis present a similar picture to an autoimmune-like disease that develops due to ICI administration (Figure 1A and C). A study noted that 128 of the 519 cancer patients (24.66%) treated with ICI developed inflammatory rheumatoid arthritis [15], and there was no sex-related difference in the incidence of this inflammatory rheumatoid arthritis caused by ICI administration [15]. Moreover, the symptoms of inflammatory rheumatoid arthritis go into remission by discontinuing ICI administration and administering steroids. In contrast, the typical symptoms of rheumatoid arthritis, which is observed in many women, do not go into remission through the administration of drugs.

Recent clinical research demonstrated that synovial fluids derived from the joints of patients with COVID-19 contained a

high number of polynuclear cells and a few mononuclear cells [16]. Furthermore, the majority of patients with COVID-19 tested negative for RF, anti-cyclic citrullinated peptide, and HLA-B27; these tests were conducted in susceptible patients or due to the severity of COVID-19 infection. Thus, the condition was compatible with inflammatory arthritis associated with COVID-19. It was further confirmed by the fact that the inflammatory arthritis in most patients with COVID-19 improved markedly after receiving combination therapy with non-steroid anti-inflammatory drugs and prednisolone [16,17,18].

Interleukin 6 (IL-6) is one of the cytokines that control humoral immunity activated by immune cells, such as T cells and macrophages. It is also involved in various physiological phenomena, including the mechanisms underlying the onset of inflammatory and immune diseases. In 1986, complementary DNA (cDNA) for IL-6 was cloned from human B cells [19]. Recent clinical evidence demonstrated that IL-6 secretion forms the backbone of hypercytokinemia seen in COVID-19-associated hyperinflammation and multiorgan failure [20]. Two types of IL-6 inhibitor drugs are approved for clinical use around the world – anti-IL-6 receptor monoclonal antibodies (e.g., tocilizumab) and anti-IL-6 monoclonal antibodies (e.g., siltuximab). These antibody medicines have been evaluated in patients with rheumatoid arthritis, juvenile idiopathic arthritis, cytokine release syndrome, and COVID-19 patients with systemic inflammation [21,22].

In summary, the inflammatory rheumatoid arthritis observed in COVID-19 patients presumably occurs due to an excessive immune response triggered by an external stimulus or infection. Therefore, the pathogenesis and histopathological findings of inflammatory rheumatoid arthritis observed in COVID-19 patients are different from those of autoimmune rheumatoid arthritis and similar to the inflammatory rheumatoid arthritis that develops as a result of ICI administration.

Abbreviations.

AIRD: Autoimmune Inflammatory Rheumatic Disease (AIRD); COVID-19: Corona Virus Infectious Disease emerged in 2019; HLA-B27: Human Leukocyte Antigen-B27; ICI: Immune Checkpoint Inhibitors; IL-6: Interleukin 6; PCR: Polymerase Chain Reaction; ReA: Reactive Arthritis; RF: Rheumatoid Factor; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus-2.

Footnote.

All authors are receiving medical ethics education. In addition, this study has been approved as a clinical medical study at each medical facility. When a patient participates in our clinical research and our medical staff collects blood, we must receive a consent form signed by the patient.

Data Sharing.

Data are available on various websites and have also been made publicly available (more information can be found in the first paragraph of the Results section).

Ethics statement.

This study was reviewed and approved by the Central Ethics Review Board of the National Hospital Organization of Japan

(Meguro, Tokyo, Japan) and the Central Ethics Review Board of Kyoto University (Kyoto, Kyoto, Japan). The approved number for this study is 50-201504. In order to carry out this research, the authors attended a research ethics education course (e-APRIN) conducted by Association for the Promotion of Research Integrity (APRIN; Shinjuku, Tokyo, Japan). The approved numbers of e-APRIN are AP0000151756, AP0000151757, AP0000151758, AP0000151769.

Disclosure.

The authors declare no potential conflicts of interest. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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Author Contributions.

T.H. performed most of the experiments and coordinated the project. T.H. and I.K. conceived the study and wrote the manuscript. T.H. and I.K. provided with information on clinical medicine and oversaw the entire study.

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