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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, შემავჯამებელი 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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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, შემავჯამებელი 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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COEXISTENCE OF APLASTIC ANEMIA AND PAROXYSMAL NOCTURNAL HEMOGLOBINURIA: DIAGNOSTIC CHALLENGES AND THERAPEUTIC STRATEGIES - CASE REPORT

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Abstract.

Aplastic anemia (AA) and paroxysmal nocturnal hemoglobinuria (PNH) are rare clonal bone marrow disorders. AA is characterized by autoimmune destruction of bone marrow stem cells and pancytopenia. In PNH, acquired genetic mutation and impaired glycoprotein synthesis leads to hemolysis and thrombus formation. The combination of both diseases represents a diagnostic and therapeutic dilemma, since increasing evidence suggests the connection between autoimmunity in AA clonal expansion of PNH.

The purpose of this publication is to illustrate the pathogenetic relationship between AA and PNH by review of available literature regarding the mechanisms of immune-mediated destruction of bone marrow and clonal expansion in combination of these hematological pathologies. A clinical case is presented as an example of this phenomenon.

Key words. Aplastic anemia, paroxysmal nocturnal hemoglobinuria, clonal expansion, eculizumab, immunosuppressive therapy.

Introduction.

Aplastic anemia (AA) and paroxysmal nocturnal hemoglobinuria (PNH) are rare bone marrow disorders with known pathogenesis. AA is characterized by immune-mediated destruction and suppression of hematopoietic stem cells with the development of bone marrow aplasia and pancytopenia [1,2]. In PNH, somatic mutations in the PIGA gene leads to complement-mediated hemolysis due to the absence of the glycosylphosphatidylinositol (GPI)-anchored surface proteins CD55 and CD59, which functions are to protect blood cells from lysis. Increasing evidence suggests a continuum between these hematopoietic disorders, especially in the context of immune selection and clonal evolution [3]. In AA, long-term bone marrow suppression provide a selective advantage for the expansion of PNH clones that are partially resistant to immune-mediated attack [4].

Aplastic anemia is a bone marrow disorder characterized by immune destruction of hematopoietic stem cells. Possible triggers may include chronic viral infections such as hepatitis B and C, parvovirus, Epstein-Barr virus and HIV, radiation, hereditary syndromes (Fanconi anemia), some toxins and drugs [5]. Immune T-cell destruction of hematopoietic stem cells is caused by CD8⁺ cells. T- cells form HLA-1 with antigens on the surface of hematopoietic stem cells and produce T-cell-mediated cytokines – TNF - alpha and interferon gamma. Interferon activates FAS/FAS l-induced apoptosis in HSCs via the release of procaspases 8 and 9 from mitochondria. As a result, the bone marrow becomes hypocellular due to the

destruction of progenitor cells. In addition, myelodysplastic syndrome can often transform into AA [6]. Moreover, due to the destruction of HSCs, clones with genetic abnormalities that are resistant to immune attack often increase in hypocellular bone marrow – such as clones with the PIGA mutation in PNH [7].

Paroxysmal nocturnal hemoglobinuria is an intravascular hemolytic disorder caused by an acquired mutation in gene on the X chromosome called the PIGA gene. This gene is required for the production of GPI-anchored protein that anchors CD55 and CD 59 to the surface of red blood cells, platelets, granulocytes and monocytes, and protects these cells from complement-activated destruction [8,9]. CD 55 inhibits C3-convertase and CD 59 blocks the membrane attack complex (MAC, C5b-9). The PIGA gene mutation occurs at the level of hematopoietic stem cells in the bone marrow. As a result, blood cells arising from the defective clones are destroyed by complement-mediated immune attack, leading to intravascular hemolysis. This process is further intensified at night, when, physiologically, respiratory rate decreases and the CO₂ level in the blood increases, causing mild respiratory acidosis. This stimulates complement activity and intravascular hemolysis develops.

Destroyed red blood cells release hemoglobin, some of which is filtered in the glomeruli of the kidneys and excreted in urine. PNH is a highly prothrombotic condition that stimulates thrombosis, especially in atypical vessels [10]. The pathophysiology involves complement-stimulated platelet activation and release of procoagulant substances, as well as direct injury to the endothelium by C3a and C5b-9. Released hemoglobin also promotes thrombosis by binding to nitric oxide (NO) [11,12]. NO is necessary for vasodilation and inhibition of platelet aggregation. As a result, vessels constrict and platelets aggregate, which further promotes thrombus formation. Endothelial injury promotes a procoagulant state by releasing tissue plasminogen factor (factor 7) and stimulating the extrinsic cascade pathway.

A close relationship between aplastic anemia and PNH is known [13,14]. In a large cohort study conducted by Fattizzo Bruno. et al. (2021), a PNH clone greater than 0.01% on granulocytes was detected in 774 people with AA, which accounted for 25% of the cohort [15]. Moreover, PNH-positive patients were noticeably younger and demonstrated more severe anemia with a median hemoglobin level of 100 g / L (range 40-170) compared to PNH-negative patients, whose hemoglobin level was 105 g / L (80-198). Patients with an increased PNH clone were found to have a lower platelet count with a median of $72 \times 10^9 / L$ (1-360) and a higher frequency of pancytopenia. In addition, elevated LDH levels were found in PNH-positive

AA patients with a median of 245 U/L (70–4614) versus 212 U/L (92–1520) in PNH-negative patients. Despite heterogeneity in primary diagnoses, patients with PNH clones at baseline were more likely to receive active treatment (78% vs. 60%) and red blood cell transfusions (76% vs. 63%). Eculizumab therapy was initiated in 133 PNH-positive AA patients.

In another study of 81 patients with AA, 58% (n=47) had PNH clones ranging from 0.01% to 97.9% [16]. Small clones of less than 1% were detected in 10% of individuals, while half of the cohort demonstrated clonal expansion greater than 10%. Eighteen patients initially had PNH-positive clones (range 0.1%–95.9%), and 5 remained persistently clone-negative throughout the follow-up period.

The coexistence of AA and PNH can be explained by clonal expansion in the aplastic bone marrow microenvironment. PNH clones in AA can exhibit variable dynamics over time, remaining stable, shrinking, or expanding with the development of clinical PNH, especially in patients with inadequate response to immunosuppressive therapy [17]. A hallmark of these clones is a deficiency of glycosphosphatidylinositol (GPI) anchors resulting from somatic loss-of-function mutations in the X-linked PIGA gene [18]. This defect renders hematopoietic stem cells (HSCs) less susceptible to immune-mediated destruction. Typically, GPI-anchored molecules present lipid antigens via CD1d, a member of the CD1 glycoprotein family on antigen-presenting cells, to T cells. In GPI-deficient clones, the absence of this structure impairs interactions with cytotoxic T lymphocytes (via TCR) and natural killer (NK) cells (via NKG2D), providing a survival advantage in the autoimmune bone marrow environment observed in aplastic anemia [19]. Furthermore, CD1d-restricted CD8⁺ T cells specific for GPI have been shown to be expanded in PNH, suggesting that GPI may act as an autoantigen and play a role in the development of bone marrow failure [20,21]. Over time, PIGA-mutated clones may accumulate additional genetic alterations that enhance their proliferative capacity and contribute to disease progression [22]. A cohort study conducted by Chen M. [23] demonstrated that in patients with severe AA who responded to immunosuppressive therapy (IST), the proportion of activated CD8⁺ T cells decreased 6 months after treatment, which was accompanied by a simultaneous decrease in the Th1/Th2 ratio. Recent studies have shown that the remission rate in patients with AA treated with antithymocyte globulin (ATG) in combination with cyclosporine reaches approximately 60%–70% (24). In 102 patients with AA, a higher remission rate was observed among patients with PNH clones, especially those whose clones appeared after IST. Among patients with PNH clones before treatment, the remission rate was 68%, which was higher than that in PNH-negative patients (56%), although the difference did not reach statistical significance, probably due to sample size limitations. This requires further verification in larger cohort studies. At 12 months after ATG therapy, patients with PNH clones had an earlier increase in hemoglobin and decrease in reticulocyte levels compared with patients without PNH clones. However, platelet recovery did not show significant differences between groups, possibly due to slower platelet recovery and the limited number of patients studied at

later time points. With regard to immune reconstitution, patients with PNH clones showed a decrease in activated CD8⁺ T cells at 6 and 12 months post-ATG, as well as a decrease in the Th1/Th2 ratio at 12 months, both trends occurring earlier than in the PNH-negative cohort. These results were consistent with clinical response patterns and suggest that AA patients with PNH clones may experience more rapid immune reconstitution, contributing to improved early therapeutic outcomes.

As shown in Figure 1, hematopoietic stem cells with PIGA mutations lack GPI- anchored protein, which disrupts the formation of HLA-I bonds by T cells and reduces autoimmune attack. Consequently, PNH clones expand and fill the aplastic bone marrow, which leads to clonal expansion.

Case presentation.

The patient, S., 59 years old, presented to emergency department of the Multidisciplinary City Hospital 1, on November 20, 2021, complaining of dark urine and general weakness.

A complete blood count revealed anemia (hemoglobin - 83 g/l), thrombocytopenia (platelets $67 \times 10^9/l$), reticulocytosis (reticulocytes 54%). Further tests showed an elevated lactate dehydrogenase level (LDH - 1388.5 U/l), and a decreased haptoglobin level (0.02 g/l).

Bone marrow biopsy (11/22/2021): bone marrow is normocellular with erythroid hyperplasia (48.4%), preserved megakaryocyte morphology and a low number of blasts (0.8%), without signs of dysplasia.

The trepanobiopsy specimen: increased cellularity (~60–65%) with erythroid islets, mild granulocytic hypoplasia, and scattered megakaryocytes, some with hypobulbated nuclei.

Results.

The pathomorphological picture of the bone marrow specimen has a number of features in favor of a hemolytic scenario for the pathogenesis of paroxysmal nocturnal hemoglobinuria.

Flow cytometry for PNH (11/24/2021) revealed a PNH clone: 94.07% on erythrocytes (CD59 type II - 92.71%, CD59 type III - 1.36%); 97.86% on granulocytes (FLAER-/CD24-); 97.74% on monocytes (FLAER-/CD14-) - a trilineage PNH clone.

Due to the lack of eculizumab, the patient received weekly red blood cell transfusions for 5 months (from November 2021 to April 2022) with development of transfusion dependence. On April 2022, due to persistent hemolysis and severe thrombocytopenia, the patient was started on eculizumab therapy at 900 mg weekly. After the first infusion, a subjective improvement in general well-being was noted.

The LDH level decreased from 1388 U to 255 U/l, reticulocytes from 54 to 2%. However, thrombocytopenia persisted ($34 \times 10^9/l$). Maintenance therapy with eculizumab continued at 600 mg/week.

On the repeat trepanobiopsy (05/25/2022): bone marrow is hypocellular with reduced granulocytic proliferation and focal erythroid hyperplasia, demonstrating mild dyserythropoiesis. Megakaryocytes are absent. In the bone marrow stroma there are areas of hemorrhage and scattered lymphoplasmacytic infiltration (Figure 2).

Cytogenetic analysis and FISH analysis: low mitotic activity and no evidence of chromosomal abnormalities, including

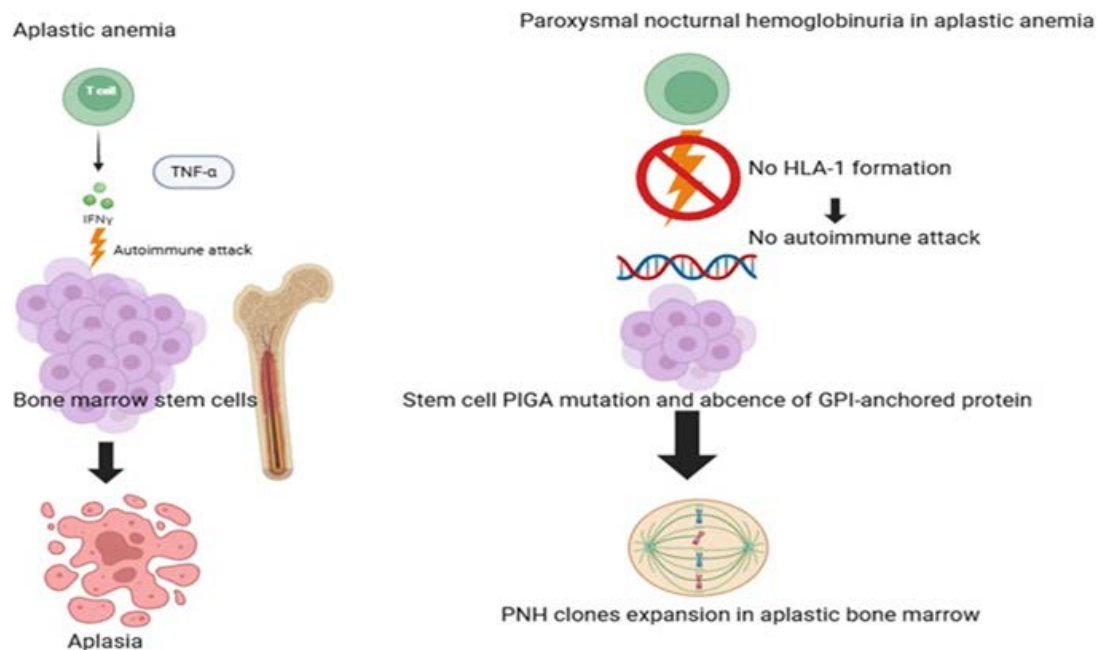


Figure 1. Immune escape of PNH clones in aplastic anemia.

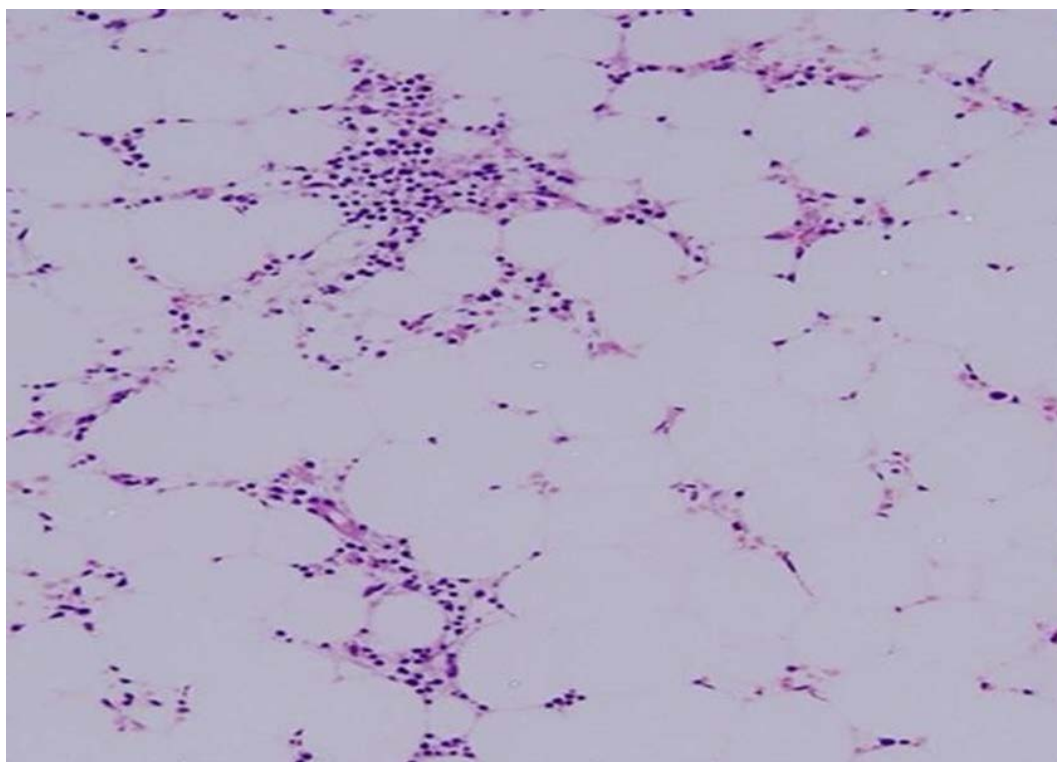


Figure 2. Trenanobiopsy specimen No. 38275. Aplastic bone marrow. Hematoxylin and eosin staining. Magnification 10x0.25.

del(7q), +20q or 5q-.

Repeat flow cytometry: granulocytes FLAER-/CD24- — 86.28%, monocytes FLAER-/CD14 — 86.5%, erythrocytes with partial deficiency of CD59 (type II) — 45.7% and complete absence of CD59 (type III) — 2.73%.

Based on a combination of clinical, morphological and cytometric data, the following clinical course was established as transition from Paroxysmal nocturnal hemoglobinuria to Idiopathic aplastic anemia Paroxysmal nocturnal hemoglobinuria overlap (AA/PNH).

From June 2022 to September 2022, the patient continued to receive eculizumab therapy and platelet concentrate transfusions. In September 2022, the patient was hospitalized in National Scientific Oncology Center (NSOC) in Astana for further examination and selection of appropriate immunosuppressive therapy. Given the lack of an appropriate allogeneic donor, the patient was prescribed combination immunosuppressive therapy (IST). The indication for IST was a combination of bone marrow hypocellularity with trilineage cytopenias confirming AA and ongoing intravascular hemolysis with a high-percentage PNH

clone, indicating PNH syndrome. Cyclosporine A (400 mg/day), ATG, and eltrombopag were added to eculizumab.

As a result of combined IST (May 2023), hematological parameters improved: hemoglobin 101 g/l, erythrocytes $3.01 \times 10^{12}/l$, leukocytes $3.7 \times 10^9/l$, platelets $59 \times 10^9/l$. Reticulocytosis remained at 35% (See Figure 3).

As can be seen from Figure 3, after the start of therapy with eculizumab and IST, the levels of hemoglobin increased over time as well as start of Eltrombopag increased platelets count, while the concentration of LDH and reticulocytosis decreased significantly.

Repeat flow cytometry data (12.05.2023): Red blood cell subpopulations 19.65% of red blood cells with CD59 type II deficiency and 6.52% of red blood cells with CD59 type III deficiency. Granulocytes with GPI deficiency (FLAER-/CD24-/CD15+) accounted for 40.4%, and monocytes (FLAER-/CD14-/CD64+) — 37.27% (Figure 4).

As can be seen from Figure 3, after the start of therapy with eculizumab and IST, the percentage of PNH clone on erythrocytes began to decrease and after a year amounted to 19.65%.

The patient currently continues maintenance therapy with eculizumab, cyclosporine A and eltrombopag without blood transfusions.

Blood work (05/19/2025): Hb 112 g, RBC $3.8 \times 10^{12}/l$, MCH- 27 pg, WBC- $4.3 \times 10^9/l$, eosinophils-1%, basophils-1%, monocytes-3%, lymph-50%, platelets $119 \times 10^9/l$.

Discussion.

As follows from this clinical observation, patient was admitted to the hematology department of Multidisciplinary City Hospital No. 1 with obvious signs of intravascular hemolysis and thrombocytopenia, as a result of which she underwent a bone marrow biopsy to exclude bone marrow pathology and flow cytometry to identify a PNH clone. A large PNH clone was detected on the surface of erythrocytes, granulocytes and monocytes. The absence of PNH clone in megakaryocytic cells, despite persistent thrombocytopenia, may indicate bone marrow failure syndrome, and not immune-mediated platelet destruction or complement-mediated lysis. For 5 months (from November to April 2022), the patient received only blood transfusion therapy (erythrocyte mass and platelet concentrate) due to the lack of eculizumab. Due to the development of transfusion dependence, eculizumab therapy was started in April 2023, which significantly reduced intravascular hemolysis, as evidenced by an increase in hemoglobin levels, a decrease in reticulocytes, bilirubin, LDH and an increase in haptoglobin, as well as the elimination of transfusion dependence. However, the lack of platelet recovery despite therapy revealed a gap between hemolytic control and hematopoiesis recovery. This prompted further research to exclude hematopoietic depression, which revealed progressive bone marrow hypocellularity, suggesting the evolution of aplastic anemia as a major factor in thrombocytopenia. Thus, the authors of several studies note that the expansion of the PNH clone in AA may reflect immune escape

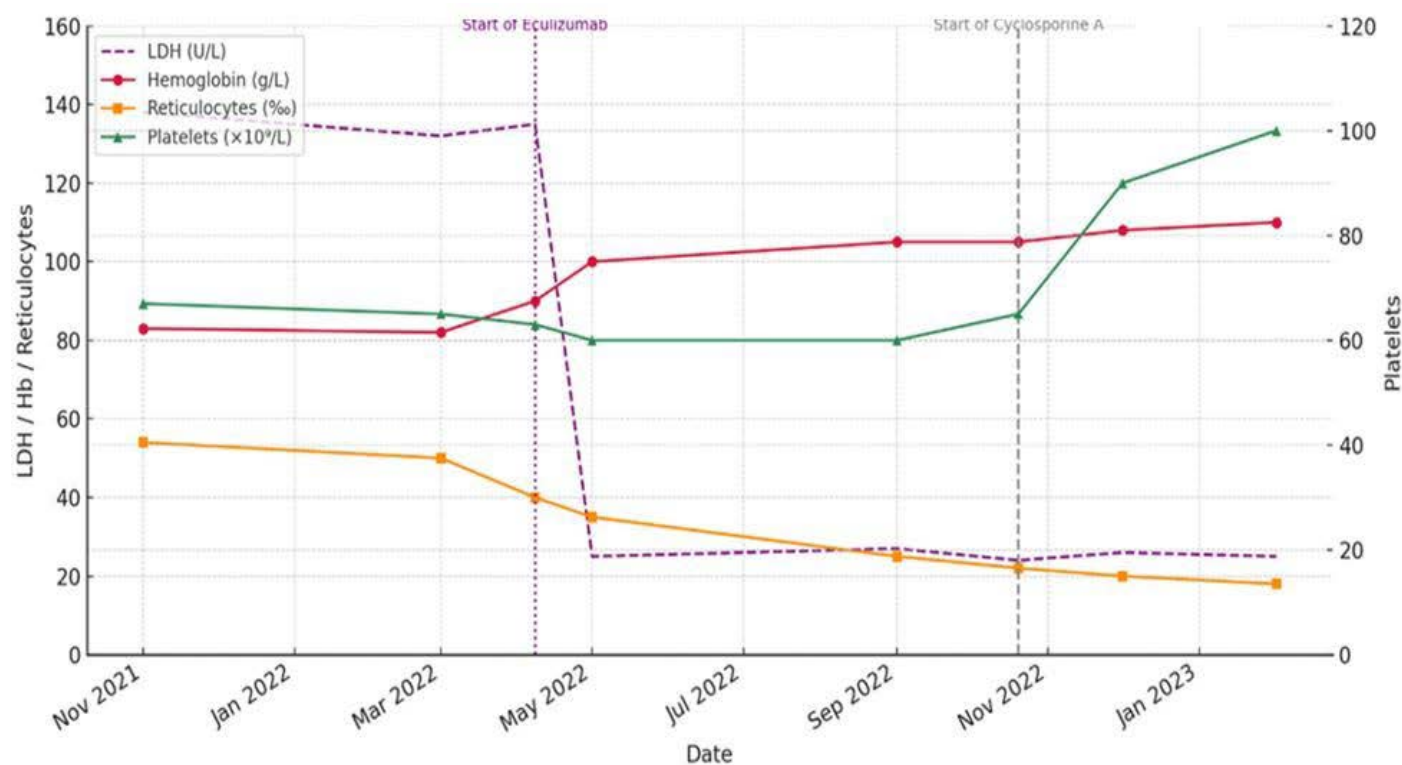


Figure 3. Dynamics of laboratory parameters before and during therapy with eculizumab and IST (cyclosporine A + ATG + eltrombopag).

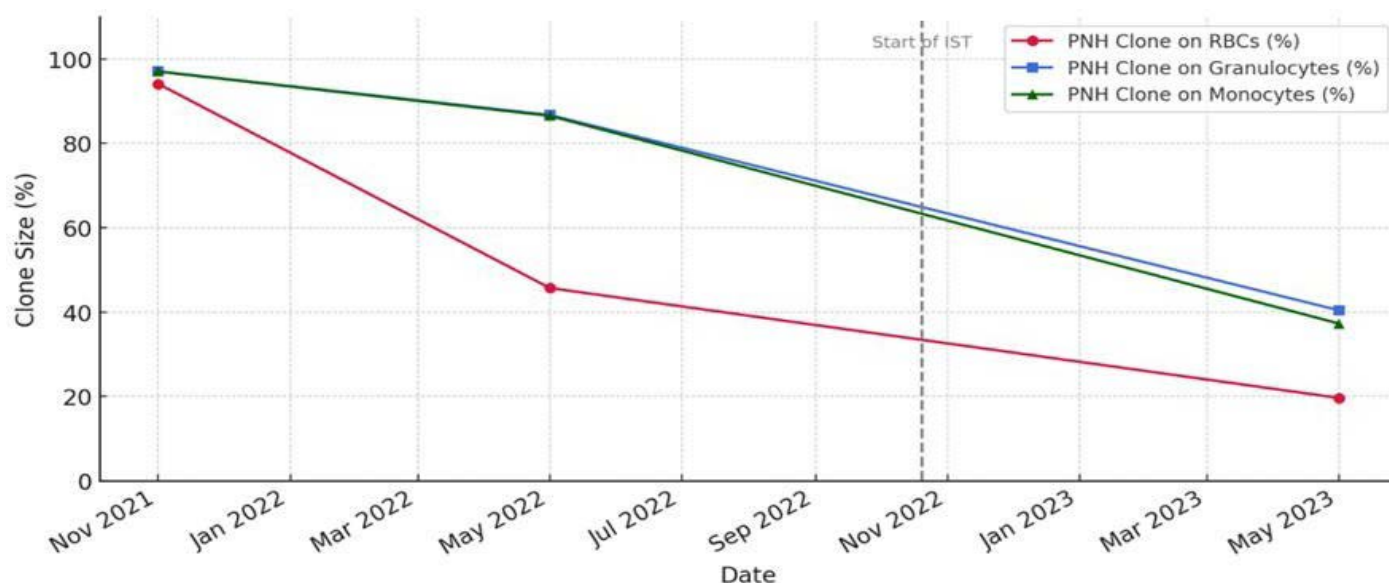


Figure 4. Dynamics of the PNH clones on erythrocytes, granulocytes and monocytes of the peripheral blood before and after combination therapy with eculizumab and IST (cyclosporine A + ATG + eltrombopag).

[24]. GPI-deficient hematopoietic stem cells (HSCs) due to PIGA mutations are protected from T cell-mediated destruction targeting normal progenitors, providing a selective advantage in the hostile immune environment of the bone marrow. However, this clonal dominance is not always permanent. In this patient, long-term therapy with eculizumab, cyclosporine A, ATG, and eltrombopag resulted in a significant reduction in the PNH clone (from 94.06% on RBCs in November 2021 to 19.65% in 2023), implying a partial restoration of immune tolerance and regeneration of normal HSCs. This observation is consistent with the literature showing that a decrease in immune pressure allows polyclonal hematopoiesis to re-establish dominance by displacing PNH-positive progenitors over time [25]. The occurrence of a high burden PNH clone in the absence of chromosomal abnormalities such as del(7q), 5q-, or +8 further supports the immune escape model rather than malignant clonal expansion, although larger PNH clones are often associated with clinical hemolysis. The persistent thrombocytopenia in patient S cannot be explained by PNH pathophysiology alone. This underscores the importance of detailed flow cytometric analysis when assessing cytopenias in patients with PNH.

It should be noted that our clinical case demonstrates the AA/PNH coexistence not as a static pathological condition, but as a consequence of the dynamics of the pathological process. The balance between clonal expansion and immune suppression may be determined by the disease phenotype and therapeutic response to specialized treatment. Although complement inhibition addresses the problem of intravascular hemolysis, it does not target the underlying bone marrow dysfunction, which may justify the need for a comprehensive treatment strategy, including immunosuppression in selected patients. The addition of eltrombopag in our patient likely facilitated the restoration of megakaryocytic lineage, which is consistent with studies that support its use in AA/PNH overlap to promote a trilineage response [26].

In summary, this case illustrates the diagnostic and therapeutic challenges of AA and PNH coexistence. It highlights the need for flow cytometry for bone marrow evaluation, particularly in cases where unexplained cytopenias persist despite targeted therapy. The reduction in PNH clone load after immunosuppression not only provides prognostic insight but also confirms the immunologic basis of the disease in many patients with coexisting syndromes.

Conclusion.

This publication highlights the complex interaction between aplastic anemia (AA) and paroxysmal nocturnal hemoglobinuria (PNH), two rare but related hematological disorders that share immune-mediated pathogenesis and clonal evolution. A review of the literature confirms that immune escape of GPI-deficient clones in the setting of T-cell-mediated bone marrow suppression plays a crucial role in the development of PNH in AA patients. Immunosuppressive therapy not only improves hematological parameters in AA, but can also influence the dynamics of PNH clones by modulating immune pressure. The presented clinical case illustrates this continuum, demonstrating how eculizumab effectively eliminates complement-mediated hemolysis, while immunosuppressive therapy with cyclosporine A, ATG and eltrombopag promotes hematopoiesis restoration and reduces the PNH clonal load.

Ethical approval and consent to participate.

Ethical approval was not required for this publication and presentation of the clinical case, as all procedures performed were part of routine clinical practice. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Informed consent.

Written informed consent was obtained from patient S. for this publication. A copy of the written consent is available for review by the journal editor upon request.

Conflict of Interest Statement.

The authors declare that they have no conflict of interest.

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