



Review

1. From Advancements to Ethics: Assessing ChatGPT's Role in Writing Research Paper

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From advancements to ethics: Assessing ChatGPT's role in writing research paper

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ABSTRACT

Artificial intelligence (AI), with its infinite capabilities, has ushered in an era of transformation in the twenty-first century. ChatGPT (Generative Pre-trained Transformer), an AI language model, has lately been in the spotlight, and there is an increasing partnership between the research authors and the chatGPT. Using ChatGPT, authors can set new benchmarks in paper writing in terms of speed, accuracy, consistency, and adaptability. ChatGPT has turned out to be an invaluable tool for manuscript writing, editing, and reference management. While it has numerous advantages, it has been criticised due to ethical quandaries, inaccuracies in scientific data and facts, and, most importantly, a lack of critical thinking skills. These disadvantages of using ChatGPT place limitations on its use in medical publications since these articles guide the future management of many diseases. While AI can fix issues, it lacks the ability to think like humans and thus cannot substitute human authors. To better comprehend the future of this technology in research, we discuss the advantages, drawbacks, and ethical dilemmas of using ChatGPT in paper writing by reviewing existing literature on Pubmed and Google Scholar and using ChatGPT itself to understand the prompt response.

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INTRODUCTION

When asked to describe itself {"Hello, tell me about yourself?"}, the ChatGPT responded, "Hello! As an AI language model, I don't have a physical form, but I'm here to help you with any questions or tasks you might have that require language processing. I was created by OpenAI, a research organisation focused on advancing artificial intelligence safely and beneficially for humanity. I was trained on a large corpus of text data from the internet, and my architecture is based on the GPT (Generative Pre-trained Transformer) framework. I'm capable of performing various language tasks, such as answering questions, generating text, summarising documents, and much more. I'm here to help you in any way I can, so please don't hesitate to ask me anything!" (Source: *OpenAI/ChatGPT*).

The launch of ChatGPT by OpenAI in November 2022 gained recognition from a global audience. It was evident immediately that this was an entirely new level of service that artificial intelligence (AI) could provide to anyone looking for information, responses, or solutions online.¹ AI uses machines to perform functions that traditionally require human intelligence, such as sensing, reasoning, learning, and problem-solving.² Under the umbrella of AI comes machine learning (ML), which means the development of algorithms that can learn from data and make predictions or conclusions without being explicitly programmed to do so. Deep learning (DL) is a subset of ML that uses multiple-layer neural networks to learn progressively complicated properties from input.³ Based on the GPT architecture, ChatGPT is a substantial language model created by OpenAI. GPT models are neural network-based language models that can produce coherent and natural language text in response to a prompt.⁴ They have been pre-trained on vast volumes of text data. The ChatGPT model is specifically created for natural language processing tasks like conversation generation, chatbots, and question-answering systems. OpenAI initially presented the GPT architecture in 2018.⁵ Since then, other large-scale language models, notably GPT-2 and GPT-3, have been created using the architecture and have demonstrated excellent performance on various language tasks. The ChatGPT model from OpenAI was first introduced in 2020 to produce human-like responses in conversational contexts.⁶ It is founded on supervised and reinforcement learning methods, which employ human trainers. Although it has been acknowledged that its solutions can still be wrong or misleading, it gained popularity among millions of users for providing extensive,

organised answers to questions on practically any topic.¹ ChatGPT can be used in various ways, like chatbots, in language translation, content generation, and answering questions on a wide range of topics, including science, history, current affairs, and many more. A recent subject of debate is the application of ChatGPT for writing medical papers. According to ChatGPT, it can help the authors streamline the writing process by assisting in the following areas:

1. Literature review: ChatGPT can assist in the literature review process by providing summaries of relevant articles, identifying key concepts and trends, and generating hypotheses for further research.
2. Manuscript writing: ChatGPT can assist in writing the manuscript by generating sections such as the introduction, methods, results, and discussion. It can also help develop a coherent and logical flow for the paper.
3. Medical terminology: ChatGPT has an extensive knowledge base of medical terminology and can provide suggestions for using appropriate medical terminology in the paper.
4. Editing: ChatGPT can help in the editing process by identifying grammatical errors, suggesting improvements in sentence structure, and ensuring the overall coherence of the paper.
5. Citation management: ChatGPT can assist in the citation management process by suggesting appropriate sources and formats for citation.

Thus, given the notable surge in chatGPT usage, this article discusses the benefits, drawbacks, and ethical considerations of employing chatGPT in research composition.

Advantages

"Hey, chatGPT, what are the advantages of using you to write scientific research papers?"

"As an AI language model trained on a vast amount of data, I can provide several advantages for writing medical research papers:

- Efficiency: I can help you save time by quickly generating high-quality content relevant to your research topic.
- Accuracy: I am designed to minimise grammar, syntax, and spelling errors. This helps ensure your medical research paper is clear and easy to read.
- Research: I can help you conduct research by suggesting relevant articles, studies, and other resources related to your research topic.
- Consistency: I can help you ensure consistency in terminology, phrasing, and formatting throughout your

medical research paper.

- Flexibility: I can adapt to your specific needs and preferences, whether you need help writing, editing, or formatting your medical research paper.” (Source: *OpenAI/ChatGPT*).

ChatGPT, within minutes, if not seconds, can generate a well-written and original article, produce a proposal requesting grants, and develop a quality improvement project just by using simple input the user gives. It is also well-versed in statistical analysis and can write codes.⁷ Macdonald et al.¹ created a simulated data set of 100,000 healthcare workers to see the rate of hospitalisation due to COVID-19 infection in workers vaccinated with the COVID-19 vaccine versus those who are not. The authors then used this fictional data to ask chatGPT to draft a paper on vaccine effectiveness, write codes, calculate hazard ratio, and perform survivor analysis.¹ In a review of literature written using chatGPT, the authors found that it can create readable content if fed with a summary using bullet points. It can also help manage the references, arrange them in order, and edit them according to the journal’s requirements.⁸ ChatGPT can quickly go through thousands of relevant published articles, summarise them, and write literature reviews, thus saving the researcher a lot of time and energy.⁹ It is also an editing and revision tool that can provide alternative and better phrasing, correct grammar, spell-check the draft, and suggest additional data to consolidate the author’s argument.¹⁰ Finally, the journals usually provide paid editing services for authors from non-English speaking countries or even in general when a paper requires editing. ChatGPT can replace those services well and perform the task with similar accuracy and at no cost.¹¹

Disadvantages and Limitations

As per ChatGPT, here are some potential disadvantages of using it in writing medical research papers:

- Lack of domain-specific knowledge: ChatGPT may not have a deep understanding of complex medical concepts or terminology specific to a particular field of medicine.

- Inaccuracy in scientific data and facts: ChatGPT generates responses based on the data it has been trained on, which may not always be accurate or up-to-date. Therefore, it may not provide accurate information for medical research purposes.

- Limited ability to interpret results: ChatGPT may not be able to analyse and interpret experimental data or results of medical research as a trained medical researcher can.

- Difficulty in identifying relevant sources: ChatGPT may be unable to identify relevant and credible sources for medical research papers. This can lead to inaccurate or unreliable information being included in the paper.

- Lack of critical thinking skills: ChatGPT does not have the ability to think critically and make informed judgments about medical research. Therefore, it may not be able to provide insights or draw conclusions based on research findings in the same way a human researcher can.

As an AI language model, ChatGPT can assist in generating text, including medical research papers; however, there are certain limitations and disadvantages to using AI-generated text in the context of medical research papers. ChatGPT might struggle to locate relevant and reputable sources for medical research articles. This may lead to inaccurate or fabricated information in the document.^{12,13} Also, ChatGPT cannot articulate its thinking or decision-making process, making it difficult to comprehend how it arrived at a specific result or detect possible flaws.¹⁴ While ChatGPT has access to a wealth of material, it may lack a thorough understanding of medical terminology, research methodology, and other domain-specific knowledge needed to write medical research publications. As a result, it may produce incorrect or unsuitable language for the target demographic. As medical research articles frequently contain complex data, statistics, and graphs that must be correctly analysed and interpreted, ChatGPT may be unable to effectively understand this data, culminating in inaccuracies in the research article.¹⁵ Unfortunately, it may also be unable to completely comprehend the context or intricacies of a particular research article, resulting in erroneous or irrelevant content being created.¹⁶ Medical students rely on their mentors to learn the fundamentals of research, but ChatGPT can take over the job of medical students, jeopardising their academic potential. While ChatGPT can create material instantly, it may not be as proficient at reviewing and revising text as a human writer. This may result in mistakes or inconsistencies in the research article. ChatGPT is based on AI and cannot substitute human knowledge and oversight in the authoring and review processes. ChatGPT can significantly alter the role of peer reviewers and editors. The partial outsourcing of editorial work to ChatGPT may have unintended effects on social and epistemic relationships within academia because editorial work plays a significant role in defining and forming epistemic communities and negotiating normative frameworks within such communities.¹⁷ A human expert in medical research may provide essential insight,

analysis, and critique of the work that an AI language model cannot replace.¹⁸ Therefore, while ChatGPT can help generate text for medical research papers, it is recommended to use it in conjunction with domain-specific knowledge and human oversight to ensure the accuracy and quality of the final product.

Ethical Implications

In our conversation with the chatGPT about the ethical implications of using it for writing medical research papers, the AI model raised the following concerns:

“If the generated text is used in a research paper, it is important to consider the intellectual property rights of the original sources. Using copyrighted material without permission or attribution can be considered unethical and may result in legal consequences.”

- “Using an AI language model like ChatGPT to write medical research papers can be seen as a form of plagiarism or academic dishonesty.”

- “Using ChatGPT to write medical research papers without the proper knowledge and expertise could potentially lead to inaccurate or misleading results, which could have serious ethical implications.”

- “Using ChatGPT to write medical research papers could also raise issues related to bias and fairness.

Language models like ChatGPT are trained on large datasets, which can potentially contain biases and prejudices that may be reflected in the generated text. It’s important to be aware of these biases and take steps to mitigate them to ensure that the research is fair and unbiased.” (Source: OpenAI/ChatGPT)

The ethical red flags this honest AI system raises are similar to what the scientific community has discussed. According to the International Committee of Medical Journal Editors (ICMJ), for someone to be classified as an author, they should have contributed substantially to the concept, design, acquisition, and analysis of data, drafted and approved the manuscript, and finally, signed an agreement that the authors are responsible and accountable for the published work.¹⁹ While submitting any paper, the authors are also required to sign a copyright transfer form.²⁰ Still, there are yet to be any policies determining the owner and copyright holder of all the text it generates, the authors or the coders who wrote the data set for ChatGPT or the company which owns it.^{21,22} When queried by ChatGPT if its name should be on the author list, it responds that since it is an AI, it is not considered to be an author. The journals require unanimous consent and final approval from all authors before publishing any manuscript; hence it is unfair and unethical on ChatGPT

to be unable to provide its consent when it is mentioned as one of the authors. The author guidelines for journals need to address these moral conundrums.

Although an advanced system, ChatGPT cannot take responsibility and be held accountable for the information it provides as many publishing services like Elsevier have come to a consensus that ChatGPT and other AI cannot be listed as the authors as it does not fulfil the ICMJ criterion.²³ The authors certify that the submitted work is original, but the big question is, “Is it?” It is not as it has been copied from ChatGPT, which is nowadays known as “AIgariism”.²⁴ By dishonouring the ethics of paper writing, students are also committing academic dishonesty by simply copy-pasting from ChatGPT, which can have severe implications for their careers in the future.¹³ Additionally, under the limitations section on the home page of Open AI’s ChatGPT, the company acknowledges that the information might be incorrect, misleading, and limited to the events before 2021 (Source: OpenAI/ChatGPT). The responses generated by ChatGPT are easy to read, look pleasing to the eye, flow smoothly, and without grammatical errors. However, it is seen that sometimes a link does not work or a citation does not exist, and there is no way for the journals to validate each reference if it slips from the reviewer or is not flagged by them during the rigorous peer review process.²⁵ All this can pave the way for misinformation and incorrect health policies formulated using this data.²⁶ Biases will always be present in any algorithm or machine humans create, and ChatGPT is no different, and neither is it claimed to be. Not only does the bias exist, but it can also amplify it. For instance, studies have shown that ChatGPT can generate biased outcomes based on sexist stereotypes, and it can favour the scientific hypothesis on which the original layers of code were trained.^{21,27} Lastly, as of March 12, 2023, ChatGPT is available at no cost for people to exploit its full potential, but it has been confirmed that this is temporary.²³ In the future, this might lead to inequalities as countries and institutes that do not have the funds and resources to sponsor will not be able to reap the benefits of the monetised model, thus widening the already existing disparities in the publishing world.¹⁷ In addition to biases and dishonesty, ChatGPT-generated text may have highly plagiarised content, sometimes exceeding the acceptable tolerance level. This is because ChatGPT generates text from its training data, and the proportionality of this plagiarism is directly related to the more commonly researched data in the field. In addition, due to large data sets and machine learning protocols, ChatGPT often threatens sensitive medical and

personal data, especially when data is shared during a conversation with ChatGPT or other AI-powered tools, or ChatGPT is being used on public servers. It becomes the moral duty of the writer to ensure the safekeeping of any sensitive data and be aware of the legal implications of using ChatGPT for academic writing.²⁸

Future

The role of ChatGPT in writing scientific papers cannot be entirely discarded, and just as the computer and internet revolutionized the world in the 20th century, this large language model (LLM) might take over research paper writing one day.²⁹ However, this will only be possible once journals and other publishing companies find out a way to detect the text generated by ChatGPT. Currently, 2 to 3 % of research papers are plagued with plagiarism, and using AI models can inflate this number.³⁰

Already existing tools like iThenticate, which are already being employed by journals, lack the capability to detect text copied from an AI interface. Still, new software is being developed to bridge this gap. The creators of ChatGPT, OpenAI, are themselves in the process of creating a detector and even launched one earlier this year, called the “classifier,” which has its own limitations and can be fooled by fraudulent authors at this stage.²⁷ Additional checkpoints like asking authors to disclose the use of AI can be used during the time of submission, and more tools and training can be provided to the editors to assist them during the editorial review process.³¹

CONCLUSIONS

AI and its resources have undoubtedly become valuable in scientific research, but they cannot fully replace researchers' critical and reflective thinking abilities. ChatGPT relies on pre-existing content and lacks the analytical capabilities of humans, such as the ability to weigh values and draw on sensory experiences to make technical and scientific decisions in the current context. While AI can aid in the processing and analysing large datasets, it cannot replace human judgment or intuition. Researchers play a crucial role in identifying meaningful patterns and interpreting the results generated by AI models. The ability of researchers to evaluate the reliability and validity of data is paramount in producing high-quality research. Furthermore, researchers possess the skill set to draw on various sources of evidence, such as experimental findings, theoretical frameworks, and

previous research, to contextualize their findings and discuss their implications. This is an essential aspect of scientific research that AI cannot fully automate. In addition, researchers are responsible for communicating their findings in a way that is both informative and engaging for the reader. The ability to articulate complex scientific ideas clearly and concisely is a skill that requires human expertise and experience. In conclusion, while AI and its resources are valuable in scientific research, they cannot replace the human expertise and experience required for interpreting results, contextualizing findings, and communicating them effectively to readers.

Conflict of Interest

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Clinical comparison of acute stroke cases with and without COVID-19

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ABSTRACT

Background We aimed to assess acute stroke cases with and without coronavirus disease 2019 (COVID-19) positivity concerning clinical features and the number of hospitalizations acute stroke cases compared to the previous year.

Methods Acute stroke patients with and without COVID-19 positivity, including those who were hospitalized in the neurology service and intensive care unit of tertiary healthcare center between 17 December 2020 and 31 January 2021 due to acute stroke, were included in this cross-sectional study.

Results Mortality ($p=0.042$) and mechanical ventilation use ($p=0.041$) were more frequent in COVID-19-positive stroke patients compared to those without COVID-19. The most common type of stroke in COVID-19-positive acute stroke patients was ischemic stroke (69.23%). Additionally, stroke patients with COVID-19 had a significantly higher percentage of kidney disease compared to those without COVID-19 ($p=0.009$). We also observed that the number of acute stroke cases hospitalized in our hospital during the pandemic decreased significantly compared to the previous year ($p=0.036$).

Conclusion Since the majority of our patients were diagnosed with COVID-19 after admission to the hospital due to stroke, it should be kept in mind that patients who apply to the hospital with stroke symptoms may also have COVID-19, even if they are asymptomatic.

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Keywords: COVID-19, acute cerebrovascular disease, stroke, symptoms



INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has affected the whole world in a very short time and still continues to exist as a public health threat. While severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is known to cause interstitial pneumonia and acute respiratory distress syndrome, there is increasing evidence that it causes encephalopathy¹, limbic and brainstem encephalitis^{2,3}, Guillain-Barré syndrome^{4,5}, and stroke (predominantly ischemic stroke, but also hemorrhagic stroke).⁶⁻¹⁰

Stroke is a serious cause of morbidity and mortality, and data concerning its incidence during the pandemic period, its association with COVID-19 infection, and its course in infected individuals are increasing.¹¹⁻¹³ Acute cerebrovascular disease, especially ischemic stroke, may occur with SARS-CoV-2.¹⁴⁻¹⁷ This study aimed to investigate acute stroke cases with and without COVID-19 positivity about the clinical features of the disease and to identify the number of hospitalisations due to acute stroke during the COVID-19 era relative to the previous year.

MATERIAL AND METHODS

According to 2022 data, the population of our city is 3,194,720. Our hospital was one of the three tertiary hospitals in our city. Additionally, there was a stroke centre in our hospital. During the pandemic between December 17, 2020 and January 31, 2021, all acute stroke patients with and without COVID-19 diagnosis were included in the study. Patients who presented to the emergency department within the first 24 hours after the onset of stroke symptoms and were diagnosed with a definitive diagnosis of stroke based on medical history, neurological examination and neuroimaging findings (brain computed tomography [CT], magnetic resonance imaging [MRI]) and hospitalised, or who underwent neuroimaging within the first 24 hours of neurological symptoms while being followed up in the hospital due to COVID-19 and were diagnosed with a definitive diagnosis of acute stroke during consultation, were included in the study.

Demographic information (age, sex, date of application), comorbid diseases (history of hypertension, diabetes mellitus, cardiovascular disease, chronic obstructive pulmonary disease [COPD], malignancy, chronic renal disease or cerebrovascular accidents), laboratory parameters at hospital admission (haemoglobin, platelet, white blood cell counts, blood glucose, urea, creatinine, erythrocyte sedimentation rate [ESR], C-reactive protein, D-dimer levels, International Normalized Ratio [INR], aPTT, and ferritin), and discharge information were prospectively recorded. Acute stroke patients with and without COVID-19 were compared in terms of demographic characteristics and laboratory results.

In addition, the number of acute stroke patients followed up in our hospital in the pandemic period (December 17, 2020, and January 31, 2021) during which the study was conducted was compared with the one-year pre-pandemic period (December 17, 2019, and January 31, 2020).

This study was approved by the local Clinical Research Ethics Committee. All protocols were conducted in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from all patients or their first-degree relatives, and only cases with informed consent were included in the study.

Statistical analysis

All analyses were performed on SPSS v21 (IBM, Armonk, NY, USA) and were evaluated for a <0.05 significance threshold for a p-value. Shapiro-Wilk test was used to check the normality of continuous variables. Continuous variables were given as mean±standard deviation in the presence of normal distribution and as median (1st-3rd quartile) in the presence of non-normal distribution. Categorical data were presented with frequency (percentage) values. Normally distributed variables were analysed with the independent samples t-test. Non-normally distributed variables were analysed with the Mann-Whitney U test. Categorical variable distributions were compared with chi-square tests or Fisher's exact test. The number of stroke cases before and after the COVID-19 pandemic was compared with the one-sample chi-square test under the null hypothesis of equal probabilities.

Table 1. Characteristics of patients with COVID-19

COVID-19 diagnosis	Frequency (%)
PCR and CT positive	14 (53.85%)
PCR negative, CT positive	11 (42.31%)
PCR positive	1 (3.85%)
Reason for hospital application	Frequency (%)
Other reasons	6 (23.08%)
Stroke	20 (76.92%)

Data were given as frequency (column percentage).

RESULTS

We included 64 patients (30 males and 34 females) with acute stroke in our study; the mean age was 70.14±14.46 (range 22 - 98) years. Twenty-six (40.63%) patients were COVID-19 positive. Fourteen (53.85%) patients were both polymerase chain reaction (PCR) test and thorax CT positive, 11 (42.31%) patients were PCR negative and thorax CT positive, and one (3.85%) patient was PCR positive only. Twenty (76.92%) COVID-19-positive patients had applied to the hospital because of a stroke. Six (23.08%) COVID-19-positive patients suffered from an in-hospital stroke, and the median stroke onset of these patients was 6

(range 1-16) days after hospitalisation (Table 1).

There were no significant differences between patients with COVID-19 negativity and positivity concerning age and sex. Renal disease percentage was significantly higher in the positive group than in the negative group (p=0.009). There were no significant differences between groups regarding other risk factors (Table 2).

The most common type of acute stroke was ischemic stroke in both groups. There were two (5.26%) transient ischemic attack cases in the COVID-19-negative group, whereas the COVID-19-positive group had one (3.85%) venous sinus thrombosis case and one (3.85%) ischemic plus hemorrhagic case.

There was no significant difference between types of stroke in groups (p=0.335). Dysarthria frequency was significantly higher in the positive group than in the negative group (p=0.003). There were no significant differences between hemiparesis (p=1.000), hemi-hypoesthesia (p=0.445), hemianopsia (p=0.525), aphasia (p=0.305), and impaired consciousness (p=0.430) of both groups (Table 2).

The groups were similar regarding Glasgow Coma Scale scores, thrombolytic/thrombectomy use (p=0.680), and need for intensive care unit stay (p=0.503). Ten (38.46%) patients were intubated in the positive group, while five (13.16%) patients were intubated in the negative group (p=0.041). Nine

Table 2. Summary of patient characteristics with regard to presence of COVID-19

Variables	COVID-19		Total (n: 64)	P-value
	Negative (n: 38)	Positive (n: 26)		
Age	72.5 (60-80)	73 (65-81)	72.5 (62-80.5)	0.477
Sex				1.000
Male	18 (47.37%)	12 (46.15%)	30 (46.88%)	
Female	20 (52.63%)	14 (53.85%)	34 (53.13%)	
Co-morbidities				
Hypertension	24 (63.16%)	16 (61.54%)	40 (62.50%)	1.000
Heart disease	20 (52.63%)	17 (65.38%)	37 (57.81%)	0.449
Diabetes mellitus	8 (21.05%)	10 (38.46%)	18 (28.13%)	0.216
COPD	8 (21.05%)	2 (7.69%)	10 (15.63%)	0.181
Malignancy	2 (5.26%)	1 (3.85%)	3 (4.69%)	1.000
Renal disease	0 (0.00%)	5 (19.23%)	5 (7.81%)	0.009
Cerebrovascular incident history	8 (21.05%)	11 (42.31%)	19 (29.69%)	0.121
Alcohol use	1 (2.63%)	0 (0.00%)	1 (1.56%)	1.000
Smoking	5 (13.16%)	3 (11.54%)	8 (12.50%)	1.000
Type of stroke				0.335
Ischemic	29 (76.32%)	18 (69.23%)	47 (73.44%)	
Haemorrhagic	7 (18.42%)	6 (23.08%)	13 (20.31%)	
Transient ischemic attack	2 (5.26%)	0 (0.00%)	2 (3.13%)	
Venous sinus thrombosis	0 (0.00%)	1 (3.85%)	1 (1.56%)	
Ischemic + haemorrhagic	0 (0.00%)	1 (3.85%)	1 (1.56%)	
Location				1.000
Anterior system	25 (86.21%)	16 (88.89%)	41 (87.23%)	
Posterior system	4 (13.79%)	2 (11.11%)	6 (12.77%)	
Stroke presentations				
Hemiparesis	28 (73.68%)	19 (73.08%)	47 (73.44%)	1.000
Hemi-hypoesthesia	17 (44.74%)	15 (57.69%)	32 (50.00%)	0.445
Hemianopsia	6 (15.79%)	6 (23.08%)	12 (18.75%)	0.525
Aphasia	13 (34.21%)	5 (19.23%)	18 (28.13%)	0.305
Dysarthria	8 (21.05%)	16 (61.54%)	24 (37.50%)	0.003
Impaired consciousness	14 (36.84%)	13 (50.00%)	27 (42.19%)	0.430
Glasgow coma scale score	14.5 (12-15)	13 (12-15)	14 (12-15)	0.229
Thrombolytic/thrombectomy	3 (7.89%)	3 (11.54%)	6 (9.38%)	0.680
Need for intensive care unit stay	16 (42.11%)	14 (53.85%)	30 (46.88%)	0.503
Intubation	5 (13.16%)	10 (38.46%)	15 (23.44%)	0.041
Mortality	4 (10.53%)	9 (34.62%)	13 (20.31%)	0.042

COPD: chronic obstructive pulmonary disease.

Data were given as mean±standard deviation or median (1st-3rd quartile) for continuous variables according to the normality of distribution and as frequency (column percentage) for categorical variables

Table 3. Laboratory measurements with regard to the presence of COVID-19

Variables	COVID-19		Total (n: 64)	P-value
	Negative (n: 38)	Positive (n: 26)		
White blood cell (x1000)	9.55 (7.80-12.20)	9.35 (6.84-11.70)	9.40 (7.65-12.10)	0.400
Haemoglobin	13.17±2.02	12.68±1.95	12.97±1.99	0.336
Platelet (x1000)	266.08±85.73	229.90±111.50	251.38±97.83	0.148
Lymphocyte (x1000)	1.67 (1.20-2.90)	1.21 (0.85-2.10)	1.55 (1.01-2.63)	0.042
Neutrophil (x1000)	6.55 (5.20-9.57)	6.16 (5.10-9.50)	6.30 (5.15-9.54)	0.758
Neutrophil/Lymphocyte ratio	4.00 (1.83-7.00)	4.76 (2.67-10.40)	4.18 (2.50-9.71)	0.232
C-reactive protein	4.85 (2.5-11.1)	29 (10.4-70)	9.8 (3.4-43.5)	<0.001
Ferritin	87.5 (42-183)	288 (125-824)	149 (50-288)	0.001
D-dimer	0.54 (0.31-1.2)	1.79 (0.65-6.35)	1 (0.4-2.43)	0.008
Blood glucose	123.5 (102-160.5)	155 (114-239)	131.5 (110-206)	0.086
Urea	36 (25-43)	40.5 (30-55)	37.5 (27.5-49)	0.119
Creatinine	0.88 (0.70-1.03)	0.80 (0.60-1.20)	0.86 (0.70-1.20)	0.661
AST	19.5 (16-23)	25 (18-40)	21 (17-28)	0.052
ALT	16.5 (11-20)	15 (11-25)	15.5 (11-22)	0.837
Sodium	138 (136-140)	139 (136-140)	139 (136-140)	0.762
Potassium	4.25 (3.90-4.50)	4.30 (3.90-4.60)	4.30 (3.90-4.50)	0.848

Data were given as mean±standard deviation or median (1st-3rd quartile) for continuous variables according to the normality of distribution and as frequency (column percentage) for categorical variables.

(34.62%) cases were mortal in the positive group, and four (10.53%) cases were mortal in the negative group (p=0.042) (Table 2, Figure 1).

Lymphocyte count was significantly lower in the positive group than in the negative group (p=0.042). C-reactive protein (p<0.001), ferritin (p=0.001) and D-dimer (p=0.008) levels were significantly higher in the positive group than in the negative group. There were no significant differences between groups concerning other laboratory measurements (Table 3).

There were 47 patients with ischemic stroke. We found no significant differences between anterior system ischemic stroke and posterior system ischemic

stroke groups regarding age, sex, hemiparesis, hemi-hypoesthesia, hemianopsia, aphasia, dysarthria, and impaired consciousness (Table 4).

When we evaluated the number of stroke cases before and after the COVID-19 pandemic, we found that the number of stroke cases was significantly higher in the pre-pandemic period compared to the post-pandemic period (110 vs 81, p=0.036). In addition, the number of ischemic strokes (90 vs 63, p=0.029) and cases with transient ischemic attack (13 vs 2, p=0.005) were significantly higher in the pre-pandemic period compared to the post-pandemic period. There was no significant difference between the

Table 4. Summary of age, sex and symptoms of patients with ischemic stroke with regard to location

Variables	Location		Total (n: 47)	P-value
	Anterior system (n: 41)	Posterior system (n: 6)		
Age	73 (65 - 80)	62 (55 - 77)	72 (61 - 80)	0.285
Sex	18 (43.90%)	4 (66.67%)	22 (46.81%)	0.398
Male	23 (56.10%)	2 (33.33%)	25 (53.19%)	
Female				
Hemiparesis	28 (68.29%)	4 (66.67%)	32 (68.09%)	1.000
Hemi-hypoesthesia	20 (48.78%)	2 (33.33%)	22 (46.81%)	0.670
Hemianopsia	8 (19.51%)	0 (0.00%)	8 (17.02%)	0.571
Aphasia	14 (34.15%)	0 (0.00%)	14 (29.79%)	0.159
Dysarthria	13 (31.71%)	4 (66.67%)	17 (36.17%)	0.170
Impaired consciousness	15 (36.59%)	0 (0.00%)	15 (31.91%)	0.157

Data were given as median (1st-3rd quartile) for continuous variables according to non-normality of distribution and as frequency (column percentage) for categorical variables.

Table 5. Comparison of stroke-related data in the pre- and post-pandemic periods

Variables	COVID-19		P-value
	Before	After	
Number of cases	110 (57.59%)	81 (42.41%)	0.036
Type of stroke			
Ischemic	90 (58.82%)	63 (41.18%)	0.029
Haemorrhagic	7 (31.82%)	15 (68.18%)	0.088
Transient ischemic attack	13 (86.67%)	2 (13.33%)	0.005
Venous sinus thrombosis	0 (0.00%)	1 (100.00%)	N/A
Need for intensive care unit stay	27 (47.37%)	30 (52.63%)	0.691

Data were given as frequency (row percentage).

pre- and post-pandemic periods in the frequency of requiring intensive care unit stay (27 vs 30, p=0.691) (Table 5).

DISCUSSION

In our study, it was observed that the majority of COVID-19-positive stroke patients were admitted to the hospital due to stroke and were diagnosed with COVID-19 through subsequent examinations. The most common type of stroke in COVID-19-positive stroke patients was ischemic stroke. COVID-19-positive stroke patients had a significantly higher percentage of kidney disease and dysarthria compared to COVID-19-negative stroke patients. There was no significant difference between the groups regarding the frequency of vascular risk factors. Intravenous

alteplase/thrombectomy treatment was applied to three patients with COVID-19 positivity. It was seen that mortality and mechanical ventilation used more common in COVID-19-positive stroke patients compared to stroke patients without COVID-19. In addition, we observed a significant decrease in the number of stroke cases hospitalised during the pandemic compared to the pre-pandemic period.

In patients with COVID-19, neurological symptoms may be the first reason for admission to the hospital. Also, patients admitted to the hospital with neurological symptoms without symptoms of COVID-19 may be diagnosed with COVID-19 in the tests performed.¹⁸⁻²² In our study, it was observed that the majority of COVID-19-positive stroke patients were admitted to the hospital due to stroke and were diagnosed with COVID-19 through subsequent tests.

It has been reported that COVID-19-positive stroke

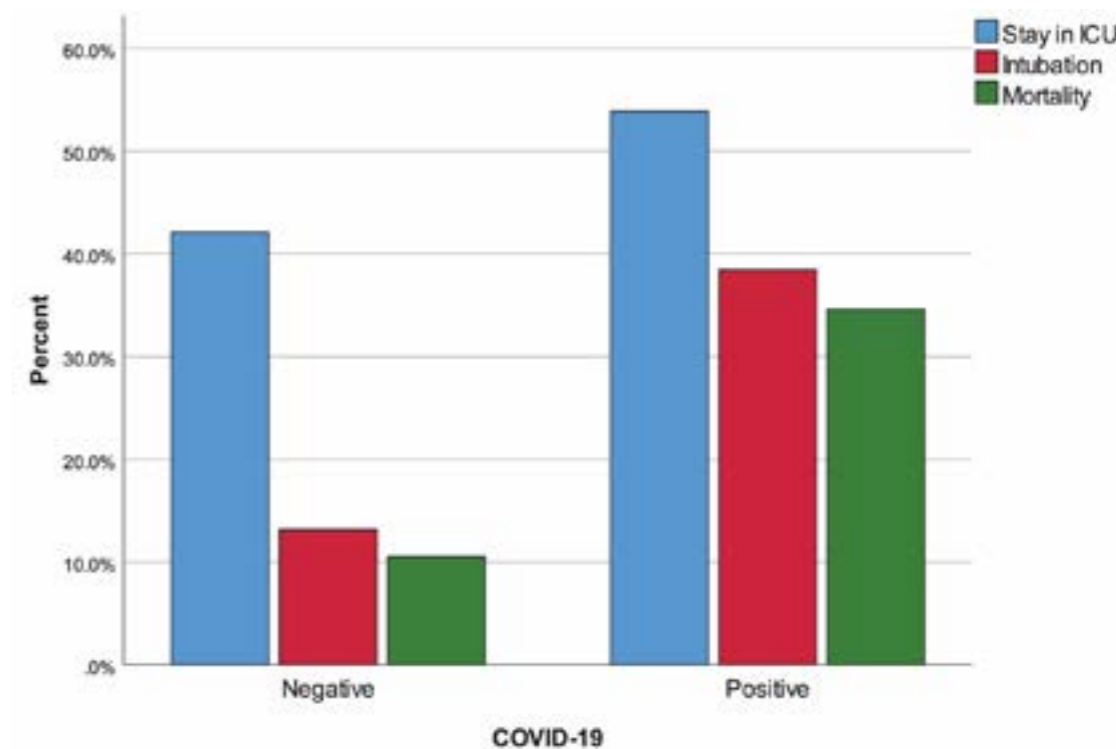


Figure 1. Intensive care unit, intubation and mortality percentages with regard to presence of COVID-19.

patients have worse outcomes, higher mortality and more frequent use of mechanical ventilation compared to stroke patients without COVID-19.²³⁻²⁴ In our study, it was seen that mortality and mechanical ventilation use were more frequent in COVID-19-positive stroke patients compared to COVID-19-negative stroke patients. The high mortality rate in COVID-19-positive stroke patients is consistent with the high mortality rate in COVID-19-positive stroke patients previously reported in the literature.^{25,26}

In addition, studies have emphasised that ischemic stroke is observed more frequently in COVID-19-positive stroke patients than other stroke subtypes.^{18,25} In our study, we observed ischemic stroke in the majority of COVID-19-positive stroke patients. Infections, especially upper respiratory tract diseases, are a risk factor for stroke. The spike protein surface unit of SARS-CoV-2 binds with high affinity to the human ACE-2 receptor, which disrupts ANG II by affecting the normal physiological function of ACE-2, thereby causing neuronal damage and endothelial cell apoptosis. The endothelial cell dysfunction, which can lead to inhibition of fibrinolysis and excessive thrombin production, plays an important role in the occurrence of thrombotic events.²⁷ In addition, COVID-19 prepares the ground for thromboembolism through many mechanisms, such as cytokine storm and hypoxia.²⁸ These may explain why ischemic stroke is more common in COVID-19 patients compared to other stroke types.

In a systematic review and meta-analysis investigating the characteristics and outcomes of COVID-19-positive stroke patients, it has been reported that COVID-19-positive stroke patients are younger, males are affected to a greater degree, and hypertension is less common compared to non-COVID-19 stroke patients. In addition, no significant difference was found in terms of previous stroke, diabetes mellitus, dyslipidemia, smoking, coronary artery disease and atrial fibrillation, while these patients had higher in-hospital mortality.²⁹

In another systematic review and meta-analysis comparing COVID-19-positive stroke patients with COVID-19-negative stroke patients, diabetes mellitus was reported to be more common in stroke patients with COVID-19 positivity.³⁰

In our study, there was no significant difference in terms of age and sex in COVID-19-positive stroke patients compared to the COVID-19-negative stroke group. The percentage of kidney disease in the positive group was significantly higher than in the negative group ($p=0.009$). In a systematic review and meta-analysis examining the incidence and outcomes of COVID-19 in patients with chronic kidney disease, it was reported that these patients were at a higher risk of having COVID-19 and had a higher risk of death due to COVID-19 compared to the general population.³¹ The groups had no significant difference regarding the frequency of other vascular risk factors.

It has been reported that there was a decrease in

applications for acute stroke during the COVID-19 pandemic.³²⁻³⁴ Our study found that the number of stroke cases hospitalised in our hospital during the COVID-19 pandemic was significantly reduced compared to the pre-pandemic period. In addition, the number of ischemic stroke and transient ischemic attack cases was substantially lower during the pandemic compared to the pre-pandemic period.

There could be many reasons for this outcome. Possible reasons leading to these results include curfews, the fact that stroke patients (particularly those with mild symptoms and clinical findings) could be refraining from applying to the hospital due to fear of exposure to COVID-19-infected individuals, the hospitals' distance from the city centre, higher selectivity regarding hospitalisation indications during the pandemic period, decreased bed count due to our institution being defined as a 'pandemic hospital', and decreases in the number of physicians working at the hospital.

There was no significant difference between the pre- and post-pandemic periods in intracranial haemorrhage and the number of patients hospitalised in the intensive care unit. Since intracranial haemorrhages are clinically more severe than ischemic strokes³⁵, these patients may be admitted to the hospital more frequently. Therefore, the number of intracranial haemorrhage cases and severe patients requiring intensive care may not have changed significantly.

Study limitations

We cannot generalise our results due to various reasons, including the fact that this was a single-centre study conducted in the early stage of the pandemic, the number of our cases was limited, and it was conducted in a tertiary institution with a specialised stroke centre which was publically defined as a 'pandemic hospital'. Due to the risk of transmission in COVID-19 patients, detailed histories may not have been obtained, and detailed neurological examinations may not have been performed. In addition, the study included patients with informed consent from stroke patients with and without COVID-19 positivity between December 17, 2020 and January 31, 2021. Not including all stroke patients hospitalised in the same period may have affected the study results.

CONCLUSIONS

Our study observed that the number of stroke patients hospitalised during the pandemic period decreased. The majority of our patients were diagnosed with COVID-19 after admission to the hospital due to stroke. For this reason, it should be kept in mind that patients who apply to the hospital with stroke symptoms during the pandemic period may have COVID-19 even if they are asymptomatic, and, if possible, COVID-19 testing should be performed.

In addition, for patients diagnosed with COVID-19, attention should be paid to the possible signs and symptoms of stroke.

Conflict of Interest

No conflict of interest was declared by the authors.

Financial Disclosure

The authors declare that this study received no financial support.

Ethical Approval

Our study was approved by the Clinical Research Ethics Committee of Bursa City Hospital (decision number: 2020-12/1, date: 16.12.2020).

Authors' Contribution

Study Conception: HB., CH., MB.; Study Design: CH., HB., MB.; Supervision: HB., CH., MB.; Funding: HB., CH., MB.; Materials: HB., CH., MB.; Data Collection and/or Processing: HB., CH., MB.; Statistical Analysis and/or Data Interpretation: HB., CH., MB.; Literature Review: CH., HB., MB.; Manuscript Preparation: HB., CH., MB. and Critical Review: HB., CH., MB.

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The effect of antifungal treatments on bronchoalveolar lavage galactomannan for the diagnosis of invasive fungal infections in patients with hematological malignancy: Single-center experience

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ABSTRACT

Background Invasive fungal infections (IFI) mainly caused by aspergillus species are one of the leading causes of death in patients undergoing immunosuppressive therapy for hematological malignancies. The presence of galactomannan in bronchoalveolar lavage fluid (BAL GM) is an important diagnostic marker. Some of the factors affecting the BAL GM are still unknown. Antifungal treatment administered before or after BAL also affect BAL GM results.

Methods To investigate the effect of BAL GM timing on the diagnosis of IFE, 100 patients receiving immunosuppressive therapy with hematological malignancy at the Uludağ University Faculty of Medicine, Hematology Department, and underwent BAL over a 3-year period with the suspicion of IFE as well as 127 BAL procedures of these patients were examined.

Results There were 70 patients who started antifungal therapy before BAL and 30 patients who did not. BAL GM was found positive in 33 (47.1%) of the 70 patients who received antifungal therapy compared to 22 (73.3%) of the 30 patients who did not receive antifungal therapy. There was a significant difference between the two groups in terms of BAL GM positivity ($p = 0.016$). Subsequently, 127 BAL procedures of these 100 patients were evaluated. When the second, third, and subsequent BAL procedures of the same patients were included in the study, BAL GM was positive in 41 (46.6%) of the 88 procedures in patients who received treatment before BAL and in 25 (64.1%) of the 39 procedures in patients who did not receive treatment before BAL. The rate of BAL GM positivity did not differ between groups ($p = 0.068$).

Conclusions The balance between reducing the risk by initiating early antifungal therapy and maximizing the diagnostic value of BAL GM should be evaluated individually for each patient.

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INTRODUCTION

Invasive fungal infections (IFIs), mainly caused by *Aspergillus* species, are one of the leading causes of death in high-risk patient groups, including patients with haematological malignancies receiving immunosuppressive therapy, and the diagnosis of IFI is fairly complex.^{1,2} The galactomannan (GM) test in bronchoalveolar lavage (BAL) is an important diagnostic method for the diagnosis of invasive fungal aspergillosis in patients with haematological malignancies.³ Guidelines generally advocate that aspergillosis be detected early and preferably before starting antifungal therapy. In clinical practice, *Aspergillus* treatment is usually initiated before bronchoscopy owing to delays caused by the patient, personnel, or equipment.⁴ Extensive studies are needed to evaluate the use of GM screening after initiating antifungal therapy. Therefore, this study aimed to assess adult patients with haematological malignancies who underwent BAL for IFI and to conduct a retrospective analysis of the effect of BAL GM timing on IFI diagnosis.

MATERIAL AND METHODS

The study included 100 patients who received immunosuppressive therapy for haematological malignancy over three years in an university department of haematology, and their BAL results were evaluated. In all cases, IFI was confirmed by clinical, microbiological, and radiological findings according to the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium (EORTC-MSGERC) diagnostic criteria.^{3,5-6} The clinical and outpatient follow-ups of the patients were reviewed retrospectively. Patient files were retrieved from the medical archive.

Bronchoscopy and bronchoalveolar lavage

According to the clinical practice guidelines of the American Thoracic Society, BAL with fiberoptic bronchoscopy was performed in all patients with a pre-diagnosis of IFI. After completing all airway examinations, BAL was performed from the bronchus/segment identified by computerised tomography (CT). BAL was collected by administering 20 mL volumes of sterile saline (maximum 100–200 mL) to the selected bronchopulmonary segment, gently aspirating each portion with the bronchoscope placed

in the wedge position, and immediately sending it to the laboratory for microbiological examination.⁷

GM antigen analysis

Optic density index (ODI) ≥ 1.0 was accepted as GM positivity in BAL results.⁶

Statistical analysis

The conformity of the data to a normal distribution was examined using the Shapiro-Wilk test. Continuous variables were presented as median (minimum–maximum) and mean \pm standard deviation. Comparisons between groups receiving antifungal therapy before and after BAL were made using the independent sample t-test. Categorical variables were expressed as n (%). Variables were compared between groups using the Chi-square, Fisher's exact chi-square, and Fisher-Freeman-Halton tests. Statistical analysis was conducted using the SPSS (IBM Corp. Release 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) program, and $p < 0.05$ was considered statistically significant in all analyses.

RESULTS

A total of 100 patients who were undergoing immunosuppressive therapy for haematological malignancy in our department over three years and 127 BAL procedures performed on these patients were evaluated. Initially, only the first BAL procedures were assessed (100 BAL procedures), and then all procedures (127 BAL procedures) performed on all patients were analysed. Of the 100 patients included, 31 were females, and 69 were males. The mean age of patients who received antifungal treatment before BAL was 52 years (21:75; 47.15 \pm 14.55), and the mean age of patients who did not receive treatment before BAL was 50 years (19:86; 45.88 \pm 18.57).

Of the 100 patients, 14 had a history of hematopoietic stem cell transplantation, three were evaluated for IFI at the time of hospitalisation for transplantation, and 83 patients had no history of transplantation. There was no significant difference between the two groups regarding age, gender, and hematopoietic stem cell transplantation ($p = 0.916$, $p = 0.647$, and $p = 0.578$, respectively) (Table 1). The haematological malignancy diagnoses of the patients were summarised in Table 2.

Patients were evaluated based on HRCT findings

Table 1. Distribution of gender, age, and history of bone marrow transplant among those receiving antifungal treatment before and after BAL

	Treatment initiated before BAL (n: 70)	Treatment initiated after BAL (n: 30)	P-value
Gender			0.916 ^a
Female	22 (31%)	9 (30%)	
Male	48 (69%)	22 (70%)	
Age	52 (21:75) (47.15±14.55)	50 (19:86) (45.88±18.57)	0.647 ^b
Hematopoietic stem cell transplantation			0.578 ^c
no history of transplantation	56 (80%)	27 (90%)	
hospitalization for transplantation	3 (4.3%)	0	
history of transplantation	11 (15.7%)	3 (10%)	

The data were expressed as n (%), median (minimum:maximum), and mean±standard deviation. BAL: bronchoalveolar lavage.

^a: Pearson Chi-square Test, ^b: Mann-Whitney U Test, ^c: Fisher-Freeman-Halton Test.

for invasive pulmonary aspergillosis. While symptoms were observed in 96 patients, 4 patients had no symptoms. Suspicious high-resolution computed tomography (HRCT) findings were detected in the entire patient group that received treatment before BAL. Micronodule was detected in 17, macronodule was detected in 12, cavitation was detected in 5, and halo was detected in 5 patients. The most common HRCT findings were consolidation and ground-glass appearance, observed in 85 patients.

It was determined that all patients were under antibiotic therapy before BAL. Antifungal prophylaxis was given to 39 patients. At the time of prophylaxis, none of the patients received antibiotic therapy. The effects of antifungal prophylaxis on BAL GM were examined in these patients. BAL GM was positive in 17 (43.6%) of the 39 patients. In contrast, BAL GM was positive in 38 (62.30%) of the 61 patients who did not receive antifungal prophylaxis. There was no difference between the groups regarding BAL GM positivity ($p=0.067$). In 35 of the patients, posaconazole was used for prophylaxis. Four patients received prophylaxis with fluconazole. BAL GM was positive in 15 (42.90%) of the 35 patients who

received posaconazole compared to 40 (61.5%) of the 65 patients who did not. There was no difference between the two groups regarding BAL GM positivity ($p=0.073$).

To understand the effect of starting antifungal treatment before BAL to reduce mortality on GM results, patients who received empiric preemptive treatment and those who did not were evaluated. In 70 patients, antifungal therapy was initiated before BAL. In contrast, 30 patients had not received antifungal therapy before BAL. Among 70 patients (some received two or more antifungal therapy regimens), 40 received classical amphotericin B, 34 received liposomal amphotericin B, eight received voriconazole, and 7 received caspofungin. BAL GM was positive in 33 (47.1%) of the 70 patients (GM median value: 2.05) who received antifungal therapy compared to 22 (73.3%) of the 30 patients (GM median value: 3.17) who did not receive antifungal therapy. There was a significant difference between the two groups regarding BAL GM positivity ($p=0.016$) (Table 3). BAL GM positivity was higher in patients who had not received antifungal treatment. Among the patients who received antifungal treatment before BAL, the

Table 2. Distribution of patients receiving antifungal treatment before and after BAL according to haematological malignancy diagnosis

Diagnosis	Treatment initiated before BAL (n: 70)	Treatment initiated after BAL (n: 30)
Acute myeloid leukemia	35 (50%)	14 (47%)
Acute lymphoid leukemia	22 (31%)	6 (20%)
Chronic lymphocytic leukemia	1 (1.5%)	1 (3%)
non-Hodgkin's lymphoma	6 (9%)	5 (17%)
Hodgkin's lymphoma	1 (1.5%)	1 (3%)
Multiple myeloma	3 (4%)	2 (7%)
Biphenotypic leukemia	1 (1.5%)	1 (3%)
Hairy cell leukemia	1 (1.5%)	0

BAL: bronchoalveolar lavage.

Table 3. Evaluation of GM positivity in patients after the first BAL procedure

BAL GM	Treatment initiated before BAL (n: 70)	Treatment initiated after BAL (n: 30)	P-value
Positive	33 (47.1%)	22 (73.3%)	0.016 ^a

GM: galactomannan, BAL: bronchoalveolar lavage.

^a: Pearson Chi-square test.

time to undergo BAL was 6 (4) (median [interquartile range]) days in BAL GM-negative patients and 5 (6) days in BAL GM-positive patients. No significant difference was found between the groups ($p=0.899$). In patients who received treatment before BAL (n: 67), no correlation was found between BAL GM level and the duration of treatment until BAL ($r=0.030$, $p=0.829$). Of the 100 patients, 36 were classified as possible, 53 as probable, and 11 as proven according to the EORTC/MSGERC diagnostic criteria.

The BAL GM results that were evaluated were from the patients' first BAL procedures. Subsequently, 127 BAL procedures on 100 patients were assessed. The following data were obtained when the second and third BAL procedures were included in the study. In the group that received treatment before BAL, BAL GM was positive in 41 (46.6%) and negative in 47 (53.4%) of the 88 procedures. In the group that did not receive treatment before BAL, BAL GM was positive in 25 (64.1%) of the 39 procedures and negative in 14 (35.9%). The rate of BAL GM positivity did not differ between patients who received antifungal therapy before BAL and those who received antifungal therapy after BAL ($p=0.068$) (Table 4).

Remission was observed in 38 of 100 patients, and eight were referred to the intensive care unit. The disease was stable in 17 patients, and 37 patients died. Among the 70 patients who started antifungal treatment before BAL, 28 had a fatal outcome, while among the 30 patients who began treatment after BAL, 9 had a fatal outcome.

DISCUSSION

Invasive aspergillosis is the most common IFI in immunosuppressed patients with haematological malignancies, particularly in patients with acute leukaemia and allogeneic hematopoietic stem cell transplantation, most commonly affecting the lungs.⁸ Therefore, early and accurate diagnosis is critical for identifying patients requiring treatment and avoiding unnecessary toxicity and costs.^{9,10} Early antifungal therapy can improve survival rates. BAL GM screening is recommended as a test that provides high-quality evidence in neutropenic patients. However, various aspects of this test need further investigation. These include the effect of antifungal therapy on this test.¹¹ Researchers emphasise the importance of conducting extensive studies to evaluate the diagnostic value of GM screening after starting antifungal therapy.⁴ In different studies, the effects of antifungal treatment on BAL GM have been reported differently. While some studies have shown that antifungal therapy adversely affects BAL GM sensitivity, others have found no significant difference, and some have seen a trend toward increased sensitivity.¹²

In a previous study involving 20 patients and 31 BAL samples, GM was negative in patients who had received amphotericin-based therapy for more than two days.¹³ In another study, BAL GM sensitivity was increased in patients receiving antifungal therapy for ≤ 2 days and decreased in patients receiving treatment for > 2 days.¹⁴ There have also been reports that active antifungal therapy reduces the sensitivity of BAL GM.⁹ However, some studies report no difference in BAL GM sensitivity between patients receiving and not receiving antifungal therapy. The mean sensitivity

Table 4. Evaluation of 127 BAL procedures in 100 patients

BAL GM	Antifungal treatment		P-value
	Treatment initiated before BAL (n: 88)	Treatment initiated after BAL (n: 39)	
Negative	47 (53.4%)	14 (35.9%)	0.068 ^a
Positive	41 (46.6%)	25 (64.1%)	

BAL: bronchoalveolar lavage, GM: galactomannan.

^a: Pearson Chi-square test.

of BAL GM was not reduced by treatment.¹⁰ Short-term antifungal agents did not affect BAL GM performance.¹⁵ It was also reported that antifungal treatment negatively affected serum GM levels but had little effect on BAL GM.¹⁶ According to one study, empiric antifungal therapy did not reduce BAL GM positivity, and patients who received antifungals for less than 48 hours had more widely positive BAL GM and higher median BAL GM levels.¹⁷ Further studies are needed to understand the diagnostic value of BAL GM after initiating antifungal therapy.^{2,4} The authors evaluated 48 patients with haematological malignancies and 62 BAL samples of these patients before and after BAL. It was reported that BAL GM results in lavages performed after the initiation of treatment were not adversely affected by the previous antifungal treatment. In contrast, a positive correlation was found associated with treatment-resistant fungal infection. Some GM results were positive even after 96 days of antifungal therapy. The authors concluded that previous antifungal treatment did not adversely affect BAL GM.⁴

The present study evaluated patients with IFI based on clinical, laboratory, and radiological findings. ODI ≥ 1 was accepted as GM positivity in BAL results. In the present study, there was no difference in BAL GM positivity between patients who did not receive antifungal prophylaxis and those who received antifungal prophylaxis before BAL. Regarding antifungal prophylaxis, there was no difference in BAL GM positivity between the two groups ($p=0.067$). In a previous study, patients who received antifungal prophylaxis and were thought to have IFI were evaluated. BAL GM was positive in 4/15 (27%) patients who did not receive prophylaxis with posaconazole and 6/11 patients (55%) who received prophylaxis with posaconazole. No significant difference was found between the groups ($p=0.227$). In contrast, the procedure was required in 15/34 patients (44%) not receiving posaconazole and 11/84 patients (13%) receiving posaconazole ($p<0.001$).¹⁸

It was determined that all patients had received antibiotherapy before BAL. In 70 patients, antifungal therapy was initiated before the first BAL procedure, whereas antifungal therapy was not initiated before the first BAL procedure in 30 patients. BAL GM positivity was higher in patients who had not received antifungal treatment. When the second and third BAL procedures of the same patients were also included in the evaluation, no significant difference was observed

between the procedures in which antifungal treatment was initiated before BAL and the procedures in which antifungal treatment was initiated after BAL, which was consistent with the findings of other studies.⁴

Our study had limitations. All patients were under antibiotics at the initiation of antifungal therapy, and the impact of this treatment on the results has not been specifically investigated. Antifungal treatment should be initiated without delay in immunosuppressed patients. Delays in BAL procedures may occur due to technical issues, personnel issues, and other reasons. The impact of administering treatment before and after BAL on outcomes is controversial, and our research contributes to the literature in this regard.

CONCLUSIONS

In conclusion, conflicting literature reports on the effect of initiating antifungal therapy on BAL GM may be attributed to differences in study methods. According to the findings obtained in the present study, BAL procedures should be performed before starting antifungal treatment whenever possible to preserve the diagnostic value of BAL GM in the first febrile episode. When repeated BAL procedures are performed on the same patient, the effect of antifungal treatment on the diagnostic value of BAL GM disappears. BAL GM is an essential diagnostic tool in haematological malignancies with IFI. The balance between reducing the risk by initiating early antifungal therapy and maximising the diagnostic value of BAL GM should be evaluated individually for each patient.

Conflict of Interest

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Ethical Approval

The protocol of the study was approved by the Medical Ethics Committee of Uludağ University, Bursa, Turkey. (Decision number: 2021-KAEK-26/173, date: 02.04.2019).

Authors' Contribution

Study Conception: MY, FÖ, BE, ED, MİK, VÖ; Study Design: MY, FÖ, BE, ED, MİK, VÖ; Literature Review: MY, FÖ, BE, ED, MİK, VÖ; Critical Review: FÖ, BE, VÖ; Data Collection and/or Processing: BE, MY; Analysis and/or Data Interpretation: MY, FÖ; Manuscript preparing: MY, FÖ.

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Acute cholestatic hepatitis due to infectious mononucleosis: A case report

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ABSTRACT

Cholestatic hepatitis is a rare complication of acute Epstein-Barr virus (EBV) infection. Here, we presented a case of acute cholestatic hepatitis secondary to acute infectious mononucleosis, who presented with complaints of abdominal pain, yellowing of the eyes and body, itching, widespread body pain, fever, nausea and vomiting. It was emphasized that EBV infection should also be considered in the differential diagnosis of cholestatic hepatitis etiology.

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Case Report

Keywords: Cholestatic hepatitis, EBV, infectious mononucleosis



INTRODUCTION

Epstein-Barr virus (EBV) is from the Herpetoviridae family. It is transmitted from person to person through close contact with the mouth, throat fluids, and bodily secretions. The virus infects pharyngeal epithelial cells and B lymphocytes and causes polyclonal B lymphocyte proliferation. Acute infectious mononucleosis caused by EBV is a disease characterised by lymphadenopathy, sore throat, fever, and positivity of heterophile antibodies in serology.¹ Cases with hepatic involvement are mostly asymptomatic, and in approximately 80-90% of these cases, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and lactate dehydrogenase (LDH) values can reach two to three times the normal value. Cholestatic hepatitis, consistent with serum alkaline phosphatase (ALP) and bilirubin differences, is rare and may occur in less than 5% of cases. In cases with liver involvement, liver enzymes usually regress to normal values within ²⁻⁶ weeks. It has been reported in the literature that there are cases of fulminant hepatitis due to acute EBV infection.²⁻⁷ Herein, a case of acute cholestatic hepatitis due to EBV is described to remind EBV infection in the differential diagnosis of cholestatic hepatitis.

CASE REPORT

A 19-year-old female patient with no known additional disease was admitted to our hospital with complaints of jaundice, itching, myalgia, abdominal pain, fever, nausea and vomiting that lasted for seven days. She applied to the gastroenterology clinic with preliminary diagnoses of acute hepatitis and cholangitis due to elevated LDH, ALP, bilirubin and liver enzymes. It was learned that she had upper respiratory tract infection complaints a week ago. There were no complaints of weight loss or night sweats. The patient's personal and family history was unremarkable. Physical examination revealed icterus in the sclera, closed traube's space, and painful lymphadenopathy with firm palpation lymphadenopathy of the right anterior cervical triangle of the neck. No pathological finding was detected in other system examinations.

In laboratory tests, she had lymphocytosis, monocytosis, increased liver disease, and hyperbilirubinemia (*Table 1*). Complete urinalysis, blood culture, and urine culture were taken from the patient with a fever of 38.8 °C. Bilirubin (2+) and

leukocyte (–) were found in the requested complete urinalysis. The patient, who had a refractory high fever, was started on intravenous hydration with 0.9% isotonic sodium chloride, ursodeoxycholic acid and paracetamol treatments, and empirical ceftriaxone 2 g/day. In the abdominal ultrasonography of the patient, the spleen was approximately 14 cm in the long axis, and no dilatation was observed in the intra-extrahepatic bile ducts. In magnetic resonance cholangiopancreatography (MRCP), the gallbladder contracted, intrahepatic and extrahepatic bile ducts were normal, and the common bile duct was not dilated. No filling defect compatible with the stone was detected in the lumen of the common bile duct, and it was observed that the pancreatic duct was not dilated. The absence of pathology in the biliary tract on imaging excluded extrahepatic cholestasis causes such as choledocholithiasis in the diagnosis.

Ceftriaxone was discontinued, and empiric piperacillin-tazobactam intravenous treatment of 4.5 g 4 times a day was started on the third day of the patient's hospitalisation, whose refractory fever continued on the third day of his treatment and whose clinical symptoms did not improve. Liver kidney microsomal antibody (LKM), anti-mitochondrial antibody (AMA), anti-smooth muscle antibody (ASMA), and anti-nuclear antibody (ANA) results of autoantibody tests were negative. Downey cells were seen in the peripheral smear of the patient whose serological examinations showed Brucella immunocapture (–), Salmonella TO (–), EBV VCA IgM (+), CMV IgM (+) (*Figure 1*). Anti-HAV IgM (0.08 S/CO; 0.8-1.2), anti-HBc IgM (0.15 S/CO; 0-1), HBsAg (0.05 S/CO; 0-1), anti-HIV (0.01 S /CO; 0-1) and anti-HCV (0.04 S/CO; 0.02-0.07) were negative. Beta-HCG was 1 mIU/mL (0-5).

The CMV DNA requested from the CMV IgM-positive patient resulted in negative. The patient's peripheral smear showed no schistocyte, and the Coombs test was negative. There was no growth in blood, urine, and stool cultures. On the seventh day of piperacillin-tazobactam treatment, macular eruptions were observed all over the body, which faded with pressure. Bacterial infections were excluded, and piperacillin-tazobactam was discontinued on the eighth day in the patient with no growth in 3 sets of blood cultures. It was observed that the rashes regressed and disappeared in the follow-up after the antibiotic treatment was discontinued.

The patient's clinical complaints were seen

Table 1. Patient's initial, highest and discharge values

Laboratory tests	Initial values	Highest values	Discharge values
Haemoglobin (g/dL) (12.1-17.2)	8.7		11.8
Lymphocyte ($10^3/\mu\text{L}$) (0.8-5.5)	5.83	6.42	4.19
Thrombocyte ($10^3/\mu\text{L}$) (150-400)	181		361
Monocytes ($10^3/\mu\text{L}$) (0.2-0.9)	0.98	1.78	0.48
LDH (U/L) (135-214)	711	825	257
ALP (U/L) (45-87)	213	434	138
Total bilirubin (mg/dL) (0.2-1.2)	12.39	18.39	2.12
Direct bilirubin (mg/dL) (0-0.3)	10.86	16.9	1.77
AST (U/L) (0-33)	120	208	36.3
ALT (U/L) (0-32)	183.2	201	67.2
CRP (mg/L) (0-5)	41.84	58.64	2.33
GGT (U/L) (0- 40)	173	179	36
INR (0.8-1.2)	1.2		0.98
Calcium (mg/dL) (8.4-10.2)	9.06		9.31
Sedimentation rate (mm/h) (0-20)	10	19	10

after an upper respiratory tract infection; she had lymphadenopathy and she had a rash with beta-lactam antibiotics. Considering the presence of lymphocytosis and monocytosis in the complete blood test, the appearance of Downey cells in the peripheral blood smear, and the positivity of EBV VCA IgM, the patient was diagnosed with cholestatic hepatitis due to acute EBV infection.

The patient continued to be followed up with intravenous hydration with 0.9% isotonic sodium chloride, ursodeoxycholic acid and paracetamol treatments. On the 10th day of the patient's follow-up and treatment, complaints of fever, jaundice, nausea, itching, and abdominal pain regressed. Decreases in liver enzyme and bilirubin levels were reported in control examinations. ALP 138 U/L (45-87), LDH 257 U/L (135-214), total bilirubin 2.12 mg/dL (0.2-1.2), direct bilirubin 1.77 mg/dL (0-0.3), C-reactive protein the patient's blood pressure level was 2.33 mg/dL (0-5), and the patient was discharged as the patient had no active complaints.

DISCUSSION

Studies on EBV show that 90-95% of adults have encountered the virus at some point in their lifetime.^{2,3} It is known that the virus, which remains in the B lymphocytes and tonsil crypt epithelial cells of seropositive individuals for life, is transmitted to seronegative people through the infected person's secretions.^{4,5} The most common symptoms in patients are nonspecific complaints such as fatigue, loss of appetite, muscle pain and headache. The classic

symptoms of infectious mononucleosis are fever, sore throat, and lymphadenopathy.^{2,8} Hepatomegaly and splenomegaly may also be seen in physical examination.^{9,10}

In 80-90% of infectious mononucleosis cases, liver enzymes usually increase twice or three times the normal level. Hyperbilirubinemia can be seen in 45% of patients and jaundice in 5%.¹¹ Cholestatic hepatitis due to EBV is a rarely reported picture. The pathogenesis of cholestasis due to EBV infection is still not fully elucidated. There are opinions that inflammation in the bile ducts is caused by the accumulation of EBV-infected activated T lymphocytes in the liver or by activating autoantibody-mediated free radicals and directly damaging hepatic cells.¹²⁻¹⁴

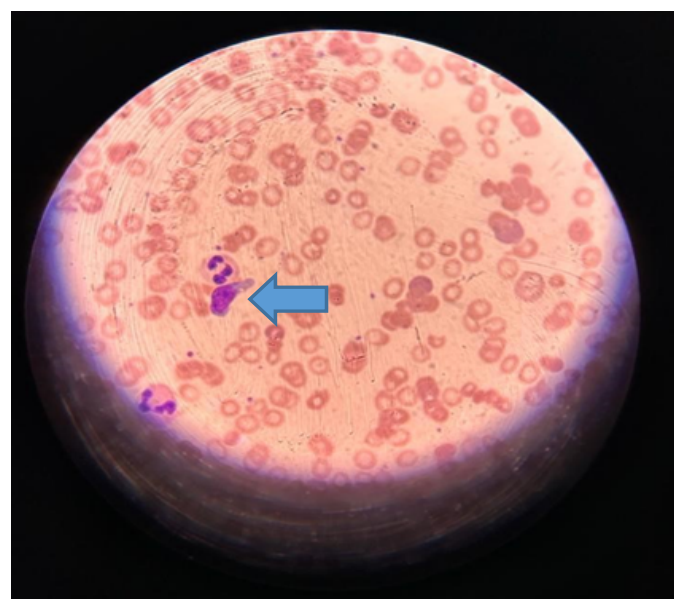


Figure 1. Downey cell seen in the patient's peripheral blood smear

The disease diagnosis is usually made by laboratory findings, clinical, heterophile antibodies, and antibodies specific to EBV.¹⁵ When cholestatic hepatitis is considered, the causes of intrahepatic cholestasis should be investigated after excluding causes of biliary obstruction such as choledocholithiasis. Hepatocellular diseases characterised by hyperbilirubinemia and cholestasis generally develop in viral infections, paraneoplastic syndromes, alcoholic hepatitis, and after using drugs such as phenytoin, erythromycin, and estrogen. Apart from primary biliary cirrhosis and gestational cholestasis, infiltrative disorders such as lymphoma, sarcoidosis, and amyloidosis are causes of intrahepatic cholestasis. In addition to hepatitis A, B, C, and E, it is known that EBV, CMV, Herpes, and rubella are also involved in the viral aetiology of intrahepatic cholestasis.¹⁶⁻¹⁹

As in our patient, anaemia and thrombocytopenia can be seen in complete blood count in infectious mononucleosis cases; however, lymphocytosis and monocytosis are frequently seen in the blood picture.³ In addition, lymphocytes known as “Downey cells” can be seen in the peripheral blood smear, with blue cytoplasm, large, and adhered around the erythrocytes.

In our case, the absence of risk factors such as alcohol use, pregnancy, medication for cholestasis, negative results of viral hepatitis etiological tests, lack of pathological appearance in the bile ducts related to stones, and obstruction in abdominal ultrasonography and MRCP directed us to further investigations and other causes. Cholestatic hepatitis due to acute EBV infection in a patient with a clinical picture compatible with infectious mononucleosis, anaemia, monocytosis, and lymphocytosis in complete blood examination, elevated liver enzymes, elevated ALP, LDH, and bilirubin, Downey cells in peripheral blood smear, EBV VCA IgM (+) diagnosis was made.

Cholestatic hepatitis due to EBV is generally a self-limiting disease with no specific treatment. In our case, after bacterial infections were excluded, antibiotic therapy was discontinued, and follow-up was continued with intravenous 0.9% isotonic sodium chloride hydration, ursodeoxycholic acid, and paracetamol symptomatic treatments. The laboratory values of the patient, who was followed up without any specific treatment other than symptomatic treatment, decreased, and her symptoms disappeared.

CONCLUSIONS

One of the causes of cholestasis is EBV infection. Therefore, if there is an increase in liver enzyme levels, ALP, LDH and bilirubin levels in a patient with fever, CMV and EBV infections should be considered in the differential diagnosis.

Conflict of Interest

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Authors' Contribution

Study Conception: HZT, OS; Study Design: YÖ, FY, PBK; Literature Review: PBK, MA; Critical Review: MA, OS; Data Collection and/or Processing: OS, YÖ; Analysis and/or Data Interpretation: FY, İB; Manuscript preparing: YÖ, OS, HÖ.

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A case of adult-onset Still's disease that does not fulfill Yamaguchi's and Fautrel's criteria: Sensitivity limitations and improvement proposal

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ABSTRACT

Adult-onset Still's disease (AOSD) is an uncommon inflammatory condition that lacks a universally accepted diagnostic test. The clinical presentation comprises symptoms such as fever, rash, joint pain, sore throat, swelling of lymph nodes, and enlargement of the liver and spleen. The diagnostic criteria developed by Yamaguchi and Fautrel are commonly employed because of their great sensitivity and specificity. However, there are cases in which individuals may not meet these criteria but still demonstrate symptoms of AOSD. In this case, we report an elderly patient who has been diagnosed with AOSD but does not meet the criteria for any of these criteria. We discussed the factors contributing to impaired sensitivity and put forth various suggestions to enhance the sensitivity of these criteria.

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Case Report

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INTRODUCTION

Adult-onset Still's disease (AOSD) is an infrequent inflammatory disease that affects multiple systems in the body. It is recognised by the clinical triad of recurrent high fever, joint pain, and a transient skin rash.¹ AOSD primarily affects young adults, particularly females. The global prevalence of this condition ranges from 0.16 to 0.40 per 100,000 individuals.¹ The precise mechanism still needs to be comprehensively understood, although the innate system is triggered, and there is an increase in pro-inflammatory cytokines such as IL-1b, IL-6, IL-8, IL-17, IL-18, and TNF-alpha.² While the exact cause of the disease is uncertain, stressful life events associated with work, family, and health could catalyse AOSD.³ The clinical symptoms of AOSD consist of recurrent high fevers, joint inflammation accompanied by joint pain and swelling, a distinct rash that is temporary, not itchy, salmon-coloured, and consists of flat or slightly raised lesions (which are uncommon in older individuals), enlargement of lymph nodes, and enlargement of the liver and spleen.³⁻⁵ The laboratory findings of AOSD include an increase in white blood cells with an increase in neutrophils, higher levels of acute-phase reactants, raised liver enzymes, and significantly elevated levels of ferritin.³ There are two globally recognised criteria for diagnosing AOSD: Yamaguchi's criteria and Fautrel's criteria (Table 1). The Yamaguchi's criteria exhibit a sensitivity of 96.3% and a specificity of 98.2%, while the Fautrel's criteria provide a sensitivity of 87.0% and a specificity of 97.8%. The Yamaguchi criteria involve

excluding other potential disorders. In contrast, the Fautrel criteria utilise ferritin and glycosylated ferritin (GF) levels as diagnostic indicators for the disease without the need for any exclusion criteria.^{6,7} In this case report, we present a patient diagnosed with AOSD, but the criteria for either of these conditions do not match. We shed light on the pitfalls of Yamaguchi's and Fautrel's criteria and how to improve them.

CASE REPORT

A 70-year-old female patient, who has been diagnosed with hypertension and is currently taking ramipril 5 mg, presented at the outpatient general internal medicine clinic with several symptoms, including a sore throat, overall fatigue, malaise, myalgia, unintentional weight loss of 5 kg over the past few weeks, widespread itchy and red skin lesions that peel off, primarily on the trunk, arms, and knees (Figure 1) as well as a fever reaching up to 38 °C. Due to the absence of any previous tick exposure or recent travel, the patient was diagnosed with a viral infection and treated conservatively. She experienced a lack of progress in the subsequent days and returned to the outpatient clinic for a second visit. The laboratory tests showed that she had normocytic anaemia and thrombocytopenia, as well as a remarkably high hyperferritinemia level of 33,511 µg/L and high C-reactive protein (Table 2). She was admitted to the internal medicine ward for further investigation due

Table 1. Two main diagnostic criteria for diagnosing adult-onset Still's disease

Criteria	Yamaguchi's criteria ⁶	Fautrel's criteria ⁷
Major	<ul style="list-style-type: none"> •Fever ≥ 39 °C lasting 1 week or more •Arthralgia lasting 2 weeks or more •Typical skin rash: maculopapular, nonpruritic, salmon-pink rash with concomitant fever spikes •Leukocytosis $\geq 10,000/\text{mm}^3$ with neutrophil polymorphonuclear proportion $\geq 80\%$ 	<ul style="list-style-type: none"> • Spiking fever ≥ 39 °C <ul style="list-style-type: none"> • Arthralgia • Transient erythema • Pharyngitis • Neutrophil polymorphonuclear proportion $\geq 80\%$ • GF proportion $\leq 20\%$ <ul style="list-style-type: none"> • Typical rash • Leukocytosis $\geq 10,000/\text{mm}^3$
Minor	<ul style="list-style-type: none"> •Pharyngitis or sore throat •Lymphadenopathy and/or splenomegaly •Liver enzyme abnormalities (aminotransferases) •Negative for RF or antinuclear antibodies 	
Exclusion	<ul style="list-style-type: none"> •Absence of infection, especially sepsis and Epstein-Barr viral infection •Absence of malignant diseases, especially lymphomas •Absence of inflammatory disease, especially polyarthritis nodosa •At least five criteria, including two major criteria and no exclusion criteria 	<ul style="list-style-type: none"> • None
		Four major criteria or three major criteria and two minor criteria

AOSD: adult-onset Still's disease, GF: glycosylated ferritin, RF: rheumatoid factor.



Figure 1. Itchy and red skin lesions that peel off, primarily on the trunk, arms, and knees

to a preliminary diagnosis of cancer, inflammatory illness, or infection. The results of Epstein-Barr virus and CMV serology tests were negative. Imaging tests of the neck, thorax, and abdomen failed to reveal any significant findings other than hepatosplenomegaly. No vegetation was observed on the echocardiography. The blood and urine cultures were negative. A skin biopsy was performed and revealed drug-related inflammation. The peripheral blood smear was insignificant. The bone marrow biopsy did not show

any evidence of neoplasia. All rheumatologic markers yielded negative results. After ruling out cancer, infections, and vasculitidis, no apparent reason could explain the significantly elevated ferritin levels. Additionally, the patient continued to experience widespread constitutional symptoms, leading to the conclusion that she likely had AOSD. She underwent assessment using Yamaguchi's and Fautrel's criteria but did not meet the requirements. Nevertheless, no probable diagnosis could account for the patient's

Table 2. Laboratory and imaging results on the first day of admission

Variables	Value	Variables	Value
Hemoglobin (g/dL)	10.9	ALT (U/L)	48
MCV (fL)	79.4	AST (U/L)	120
Leukocyte (/ μ L)	7,080	ALP (U/L)	61
Neutrophil (/ μ L)	5,130	GGT (U/L)	42
Lymphocyte (/ μ L)	820	Total bilirubin (mg/dL)	0.50
Thrombocyte (/ μ L)	65,000	BUN (mg/dL)	17
ESR (mm/h)	2	GFR (mL/min/1.73 m ²)	53
CRP (mg/L)	83.6	Creatinine (mg/dL)	1.05
LDH (U/L)	1109	Sodium (mmol/L)	136
Ferritin (μ g/L)	33511	Potassium (mmol/L)	3
Iron (μ g/dL)	33	Uric acid (mg/dL)	6.4
Transferrin saturation (%)	16.1	Total protein (g/dL)	5.7
Fibrinogen (mg/dL)	172	Albumin (g/dL)	3.5
Hemolysis markers	Negative	Triglyceride (mg/dL)	391
Viral serology	Negative for HSV, Parvovirus B-19, EBV, CMV, hepatitis viruses		
Urine, blood and throat cultures	All negative		
Thorax CT	No lymph node, no nodule or mass, no sign of infection		
Abdominal CT	Hepatomegaly (170 mm), splenomegaly (142 mm), no lymph nodes		
Peripheral blood smear	Normal erythroid lineage, no sign of myelodysplasia, lymphocyte abnormality		
Bone marrow biopsy	Hypercellular bone marrow. 80% cellularity ratio; mildly increased megakaryocyte count; no sign of neoplastic infiltration		

ALP: alkaline phosphatase, ALT: alanine aminotransferase, AST: aspartate aminotransferase, BUN: blood urea nitrogen, CMV: cytomegalovirus, CRP: C-reactive protein, CT: computed tomography, EBV: Epstein-Barr virus, ESR: erythrocyte sedimentation rate, GFR: glomerular filtration rate, GGT: gamma-glutamyl transferase, HSV: herpes simplex virus, LDH: lactate dehydrogenase, MCV: mean corpuscular volume.

Table 3. Laboratory results prior to discharge

Variables	Value	Variables	Value
Hemoglobin (g/dL)	10.5	ALT (U/L)	23
MCV (fL)	79.5	AST (U/L)	18
Leukocyte (/μL)	8,840	ALP (U/L)	56
Neutrophil (/μL)	6,500	GGT (U/L)	29
Lymphocyte (/μL)	1,320	Total bilirubin (mg/dL)	0.50
Thrombocyte (/μL)	141,000	BUN (mg/dL)	14
ESR (mm/h)	2	GFR (mL/min/1.73 m ²)	63
CRP (mg/L)	<2	Creatinine (mg/dL)	0.9
Ferritin (μg/L)	589	Sodium (mmol/L)	140
Iron (μg/dL)	40	Potassium (mmol/L)	4.6
Transferrin saturation (%)	16.3	Uric acid (mg/dL)	5.1
Albumin (g/dL)	3.8	Triglyceride (mg/dL)	156

ALP: alkaline phosphatase, ALT: alanine aminotransferase, AST: aspartate aminotransferase, BUN: blood urea nitrogen, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, GFR: glomerular filtration rate, GGT: gamma-glutamyl transferase, MCV: mean corpuscular volume.

clinical and laboratory findings. As a result, she was diagnosed with AOSD and started on a regimen of methylprednisolone 24 mg. She was then discharged with close follow-up. Two weeks later, she was evaluated at the outpatient clinic, and her ferritin levels significantly decreased. Her fever, myalgia, malaise, and fatigue symptoms also reduced considerably. The rheumatology department commenced the use of methotrexate along with a tapering plan for methylprednisolone. After a month, her ferritin level decreased to 589 μg/L, and she described her general health as “exceptionally well.” Her last laboratory results were shown in Table 3. She is currently taking a weekly dosage of 10 mg of methotrexate.

DISCUSSION

AOSD is a rare condition with an unknown aetiology, characterised by persistent fever, polyarthritis, and rash. Diagnosis is typically established by excluding malignancies, rheumatological disorders, and infections using either Yamaguchi's or Fautrel's criteria.^{6,7} The patient presented in this case report did not fulfil any of the criteria above yet was correctly diagnosed with AOSD, and the patient experienced remission with the appropriate treatment. We acknowledge that no criteria can have 100% sensitivity, but we identified several possible causes that lower the sensitivity of these criteria.

Firstly, having a fever of 39 °C and over is a major criterion according to the Yamaguchi and Fautrel criteria^{6,7}, a finding our patient lacks. It has

been shown that fever tends to be lower in older people compared to youngsters.⁸ Although no mean age data exists in Yamaguchi's article, in Fautrel's cohort, consisting of 72 patients, the mean age was 35.2±13.5. Moreover, a study by Kim et al.⁹ illustrated that only 30% of patients with Still's disease had a fever of 39 °C. A case-based review illustrated that fever was not present in 23.9% of elderly patients (mean age 75) with AOSD but without macrophage activation syndrome (MAS).¹⁰ The markedly lower age of patients in Fautrel's diagnostic criteria and the fact that fever response is blunted as age increases point out the necessity of revising the fever threshold according to age.

Another major criterion of Yamaguchi's criteria is the presence of typical non-pruritic maculopapules described as salmon-pink-colored. Our patient's rash manifested as peeling red lesions with itching. Considering various examples in the literature that show the occurrence of rashes in different variations^{11,12} and a lower incidence of typical rash in older people⁴, it might be advisable to broaden the criteria to encompass all dermatological lesions. An observational study demonstrated that the prevalence of atypical skin lesions was 14%, with persistent pruritic papules and/or plaques constituting the most frequent non-classical skin findings.¹³ While this addition might slightly lower the specificity of the criteria, it is expected to increase the sensitivity significantly.

The major criterion of arthralgia lasting more than two weeks has not been observed in our patient. Instead, the patient reported general, widespread

pain throughout the body. Although we did not encounter a patient in the literature who did not report arthralgia but stated widespread body pain, a patient, later diagnosed with AOSD, from India describing polyarthralgia persisting for 18 months is the most similar presentation to our patients.¹⁴ Moreover, it was shown that more than 25% of elderly patients with AOSD but without MAS did not experience arthralgia or myalgia at all.⁹ Generalised body pain may not be expected to become a major or minor diagnostic criterion; further registries should involve widespread body pain to determine its role in diagnosis.

The last point is that glycosylated ferritin can be used as a bioindicator. Although GF has 89% specificity and 63% sensitivity for AOSD¹⁴, it is an expensive and relatively challenging test. Moreover, it is not widely available. Therefore, including this exceptional test in the minor rather than the major criteria may be prudent.

CONCLUSIONS

In conclusion, this case report demonstrated that, despite the high sensitivity and specificity of Yamaguchi's and Fautrel's criteria, their performance may be limited in elderly patients. Age-dependent modifications, both for fever and rash, may improve the sensitivity and specificity of these criteria.

Consent

Consent has been obtained prior to manuscript preparation

Authors' Contribution

Study Conception: ATG, BH, BK, NŞ, AÖ, TIG,; Study Design: ATG, BH, BK, NŞ, AÖ, TIG,; Literature Review: ATG, BH, BK, NŞ, AÖ, TIG,; Critical Review: ATG; Data Collection and/or Processing: ATG, BH, BK, NŞ, AÖ, TIG,; Analysis and/or Data Interpretation: ATG, BH, BK, NŞ, AÖ, TIG,; Manuscript preparing: ATG, BH, BK, NŞ, AÖ, TIG.

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