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# Evaluation of non-preoperative chest diseases consultations

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## ABSTRACT

**Aims:** This study was conducted to evaluate non-preoperative patients in the chest diseases department of the training and research hospital.

**Methods:** 990 patients were evaluated retrospectively between 01.10.2023 and 01.03.2024 in Ankara Training and Research Hospital, Department of Chest Diseases. The services that requested consultation and the reasons for the request, the patients' comorbidities, chest radiography and, when deemed necessary, the requested lung computed tomography were examined. The data obtained was analyzed with IBM SPSS (Statistical Package for Social Sciences). As descriptive statistics, mean±standard deviation and median (minimum-maximum) were given for quantitative variables, and number (percentage) was given for qualitative variables.

**Results:** Within the hospital, 990 non-preoperative chest diseases consultations were requested within a 6-month period. Those younger than 18 years of age, those who were to be evaluated preoperatively, and those who were asked for consultation from the pulmonology department but did not attend the evaluation were excluded from the study. The average age of the patients for whom consultation was requested was 69.12±16.07 years. 52.1% of the patients were female and 47.9% were male. 470 (47.5%) of the patients were smokers. Among the services where consultation was requested, the first services were 163 (16.5%) emergency services, 129 (13.0%) emergency intensive care units and 112 (11.3%) infectious diseases. 398(40.2%) patients had shortness of breath. It was observed that 411 (41.5%) patients had DM, 285 (28.8%) patients had hypertension, and 108 (10.9%) patients had heart failure. While chest radiography was requested for all patients for whom consultation was requested, 570 (57.6%) thorax computed tomography scans were performed when deemed necessary.

**Conclusion:** Chest diseases consultations is performed mostly for diagnostic support and treatment recommendation. In our study, patients were included retrospectively. In retrospective studies, it is of great importance to keep proper records in consultations and to take a complete examination and anamnesis. However, unnecessary requested chest diseases consultations brings a serious workload.

**Keywords:** Pulmonary diseases, consultation, non-preoperative evaluation

## INTRODUCTION

It is inevitable for more than one medical department to work together in order to approach a patient holistically. Consultation is defined as scientific and technical assistance or counseling received by the primary physician who follows and treats a patient from physicians working in a different field.<sup>1</sup> Chest diseases is among the departments where consultation is requested most frequently from other departments.

Chest diseases consultation is requested from all clinical branches due to the diagnosis and treatment of any pathology involving the respiratory system, evaluation of preoperative patients in terms of the respiratory system, and postoperative pulmonary problems. Article 19 of the Turkish Medical Association's Code of Ethics for the Profession of Medicine describes the requesting and responding to consultations in

detail.<sup>2</sup> One of the guidelines published on this subject was published at Bülent Ecevit University Faculty of Medicine.<sup>3</sup> However, most physicians cannot comply with the guidelines on consultation in routine due to busy working conditions and lack of time.

## METHODS

This study was performed retrospectively by examining the consultations requested for 990 patients in the Department of Chest Diseases between October 01, 2003 and March 01, 2024 in Ankara Training and Research Hospital. Approval was obtained from Ethical Committee of Faculty of Medicine, Ankara University (Date:21.09.2023, Decision No: 22499618). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Consultations from inpatient units were also included in the study. The clinic where the consultation was requested, demographic data of the patient, symptoms, smoking habits, comorbidities, postero-anterior (PA) chest radiography, C-reactive protein (CRP), specific and nonspecific culture of sputum, routine hemogram, sedimentation and biochemistry findings, arterial blood gas findings were recorded. Anamnesis was obtained from relatives of patients who were unable to give anamnesis. Advanced radiologic examinations such as thorax computed tomography (CT) were added to the orders when deemed necessary. Statistical analysis was performed with the data obtained.

## RESULTS

In a 6-month period, 990 preoperative external chest diseases consultations were requested. Those younger than 18 years of age, those who were to be evaluated preoperatively, and those who were asked for consultation from the pulmonology department but did not attend the evaluation were excluded from the study. The mean age of the patients for whom consultation was requested was  $69.12 \pm 16.07$  years. 516 (52.1%) were female and 474 (47.9%) were male. 470 (47.5%) of the cases were smokers. Non-smokers were 355 (34.89%). 175 (17.7%) patients had quit smoking. In non-preoperative consultations, the emergency department ranked first with 163 (16.5%) patients, followed by emergency intensive care with 129 (13%) and infectious diseases with 112 (11.3%) patients (Table 1).

**Table 1. Clinics requesting chest diseases consultation**

Clinic	n	%
Emergency service	163	16.5
Emergency intensive care	129	13.0
Infectious diseases	112	11.3
Neurology	57	5.8
Orthopedics	51	5.2
General surgery	45	4.5
Nephrology	44	4.4
General internal medicine	43	4.3
Anesthesiology intensive care	34	3.4
Cardiovascular surgery intensive care	31	3.1
Cardiovascular surgery	29	2.9
Neurosurgery intensive care	28	2.8
Cardiology	26	2.6
Internal medicine intensive care	26	2.6
Neurosurgery	25	2.5
Dermatology	21	2.1
Neurology intensive care	20	2.0
Gastroenterology	19	1.9
Romatology	16	1.6
Cardiology intensive care	12	1.2
Endocrinology and metabolism	11	1.1
Urology	11	1.1
Eye diseases	11	1.1
Ear nose throat	9	0.9
Gynecology and obstetrics	9	0.9
AMATEM*	3	0.3
Surgical oncology	3	0.3
Plastic surgery	2	0.2
Total	990	100.0

\*AMATEM (Research, Treatment and Training Center for Alcohol and Substance Dependence)

The most common symptom was dyspnea with 398 (40.2%) patients. The second most common symptom was chest pain with 232 (23.4%) patients and the third most common symptom was cough with 165 (16.7%) patients (Table 2).

**Table 2. Symptoms of patients for whom chest diseases consultation was requested**

Symptoms	n	%
Dyspnea	398	40.2
Chest pain	232	23.4
Cough	165	16.7
Phlegm	75	7.6
Hemoptysis	54	5.5
Fever	46	4.6
Other	20	2.0
Total	990	100.0

In terms of comorbidities, 411 (41.5%) patients had diabetes mellitus, 285 (28.8%) had hypertension, and 108 (10.9%) had heart failure (Table 3).

**Table 3. Co-morbidities of patients for whom chest diseases consultation is requested**

Additional diseases	n	%
Diabetes mellitus	411	41.5
Hypertension	285	28.8
Heart failure	108	10.9
Chronic obstructive pulmonary disease	46	4.6
Pneumonia	31	3.1
Renal failure	30	3.0
Asthma	25	2.5
Other cardiac diseases	16	1.6
Neurologic diseases	12	1.2
Thyroid diseases	10	1.0
Dermatology diseases	10	1.0
Gastrointestinal diseases	6	0.6
Total	990	100.0

All of the patients had chest radiography and thorax CT was performed in the patients who were deemed necessary. Chest X-ray findings were within normal limits in 80 (8.1%) patients. The most common findings on chest radiography were consolidation in 203 (20.5%) patients, hilar fullness in 146 (14.7%) patients and increased bronchovascular arborization in 110 (11.1%) patients (Table 4).

Thorax CT was performed in 570 (57.6%) patients. Thorax CT findings were within normal limits in 148 (14.9%) patients. The most common findings on thorax CT were consolidation in 81 (8.2%) patients ground glass appearance in 45 (4.5%) patients and increased pleural effusion in 43 (4.3%) patients. (Table 5).

CT angiography was performed in 104 (10.5%) patients with suspected pulmonary embolism in whom dimer was ordered. Pulmonary embolism was detected in 24 (2.4%) patients who underwent CT angiography.



Chest X-ray findings	n	%
Consolidation	203	20.5
Hilar fullness	146	14.7
Increased bronchovascular arborization	110	11.1
Normal	80	8.1
Increased aeration	79	8.0
Reticulo linear density increase	71	7.2
Pleural effusion	69	7.0
Atelectasis	66	6.7
Interstitial involvement	64	6.5
Nodule	33	3.3
Sinus blunting	28	2.8
Diaphragm elevation	15	1.5
Mass	14	1.4
Flattening of the diaphragm	12	1.2
Total	990	100.0

Thorax CT findings	n	%
No CT scan	420	42.4
Normal	148	14.9
Consolidation	81	8.2
Ground glass appearance	45	4.5
Pleural effusion	43	4.3
Mediastinal lymph adenopathy	35	3.5
Reticulo linear density increase	35	3.5
Atelectasis	34	3.4
Pulmonary embolism	24	2.4
Malignancy	22	2.2
Cavity	19	1.9
Cyst	16	1.6
Thickening of the pleura	16	1.6
Mass	14	1.4
Bronchiectasis	13	1.3
Nodule	13	1.3
Emphysema	12	1.2
Total	990	100.0

CT: Computed tomography

The most common reasons for consultation were respiratory symptoms in 274 (27.7%) patients, radiologic reasons in 209 (21.1%) patients and desaturation in 193 (19.5%) patients (Table 6).

After consultation, 109 (11.0%) patients had normal pulmonary findings. The most common diagnoses were respiratory failure in 213 (21.5%) patients, followed by COPD exacerbation in 144 (14.5%) patients and pneumonia in 133 (13.4%) patients (Table 7).

Reason for requesting consultation	n	%
Respiratory symptoms	274	27.7
Radiological causes	209	21.1
Desaturation	193	19.5
D-dimer increase	104	10.5
Request for oxygen concentrator and nebulizer	84	8.5
Physical examination findings	49	4.9
Consent for medication (rheumatology and dermatology)	49	4.9
For CPAP, BIPAP and mechanical ventilation needs	28	2.8
Total	990	100.0

CPAP: Continuous positive airway pressure, BIPAP: Bilevel positive airway pressure

Diagnosis	n	%
Respiratory failure	213	21.5
Chronic obstructive pulmonary disease exacerbation	144	14.5
Pneumonia	133	13.4
Normal lung	109	11.0
Pulmonary embolism	83	8.4
Heart failure	79	8.0
Pulmonary hypertension	70	7.1
Pleurisy	63	6.4
Asthma exacerbation	61	6.2
Lung cancer	18	1.8
Interstitial lung disease	10	1.0
Lung metastasis	7	0.7
Total	990	100.0

## DISCUSSION

The physician requesting consultation is asked to provide information about the patient and clearly state the request for help. The physician responding to the consultation should also write down the patient's complaints, comorbidities, physical examination, and recommendations clearly and comprehensibly.<sup>4</sup> Contrary to the studies stating that the most common reason for requesting a GCT was for preoperative evaluation, Zamani<sup>5</sup> and Uçar et al.<sup>6</sup> reported that 61% of GCTs were requested for non-preoperative reasons.<sup>5,6</sup> Karnak et al.<sup>7</sup> found that most consultations were performed by internal departments to contribute to the diagnosis and to obtain treatment recommendations 61.4%.

When the patients included in the study were evaluated according to gender, Çakmak et al.<sup>8</sup> In a study in which more than 5000 GCTs were analyzed, it was found that 58% of male patients were asked for more consultation. The fact that men smoke more and that lung cancer and COPD are associated with smoking shows such a result. In our study, there were 516 (52.1%) more female patients. Advanced age, especially over 70 years, is an important risk factor that increases postoperative morbidity and mortality.<sup>5,9,10</sup> In our study, the mean age was 69.12±16.07 years.

Smoking increases preoperative mortality and postoperative pulmonary complications. The risk is high even in patients

without chronic lung disease.<sup>11</sup> In our study, 470 (47.5%) patients were smokers.

Karnak et al.<sup>7</sup> found dyspnea 63%, cough 58%, sputum 47%, chest pain 27%, hemoptysis 4% in their study. Zamani et al.<sup>5</sup> found dyspnea 32%, cough 29%, sputum 22%, chest pain 9%, hemoptysis 2%. Annakkaya et al.<sup>12</sup> found these rates to be 30%, 33%, 23%, 5%, 3%, respectively; Öztürk et al.<sup>13</sup> found these rates to be 58%, 20%, 8%, 9% and hemoptysis 5%. In our study, dyspnea was the most common symptom in 40.2% of 398 patients. While taking anamnesis of the patients, especially the patient's age, respiratory symptoms and smoking history should be questioned.<sup>5</sup>

In our study, 398 (40.2%) patients were most commonly referred for ILC due to dyspnea. While dyspnea was the most common reason for consultation in the study by Arslan et al.,<sup>13</sup> cough was the most common reason for consultation in the study by Öztürk et al.<sup>14</sup> In our study, the most common reason for consultation was respiratory symptoms (n:274; 27.7%). Respiratory failure was the most common group consulted (n:213; 21.5%).

In preoperative and asymptomatic patients with lung disease, chest radiography is not routinely performed under the age of 60 years. In the presence of history and physical examination findings indicating cardiac or pulmonary disease, in suspicion of metastasis in a patient with cancer, before thoracic surgery, and in regions with a high incidence of tuberculosis, PA chest radiography is recommended. In other studies conducted in our country, it was observed that PA chest radiography was requested in all patients.<sup>12,13</sup> In our study, PA chest radiography was performed in all patients and 80 (8.1%) patients had normal chest radiography. Thorax CT was performed in 570 patients and lung findings were found to be normal in 148 (14.9%) patients who underwent thorax CT.

In non-preoperative consultations, risk factors that play a role include the presence of lung disease, age, smoking, obesity.<sup>14</sup> In non-preoperative consultations, pulmonary complications include respiratory failure, pneumonia, bronchospasm, atelectasis and exacerbation of existing chronic lung disease.<sup>7,14</sup> In our study, we observed respiratory failure, COPD and pneumonia, respectively.

COPD is an important factor that plays a role in the development of postoperative pulmonary complications.<sup>5,15</sup> It is known that the rate of postoperative atelectasis in patients with COPD is 25-70%.<sup>15</sup> Mortality rates are known to be 0-8% according to various references.<sup>16,17</sup> In a group of patients with COPD who underwent major surgical intervention, complications developed at a rate of 29%. While the incidence of postoperative pulmonary complications is 5-10% in healthy individuals, it is 25-90% in COPD patients.<sup>18</sup> The risk of respiratory failure in patients with severe COPD is 5%, and the risk of complications increases significantly in hypercapnic patients.<sup>19</sup> In our country, COPD was found to be 31.6% among the results of chest diseases consultations.<sup>5,6,12</sup> Karnak et al.<sup>7</sup> found COPD rate to be 31.4%, Zamani<sup>5</sup> 27.1%, Uçar et al.<sup>6</sup> 22%, Annakkaya et al.<sup>12</sup> 14%, Arslan et al.<sup>13</sup> 36%. In our study, the number of consultations followed and treated with the diagnosis of COPD, which ranked second after respiratory failure, was 144 (14.5%). In studies, the rate

of chest diseases consultations due to asthma varies between 1.4-14.5%.<sup>14,20,21</sup> In our study, the number of patients with asthma was 61 (6.2%).

The rate of hospitalization due to pneumonia is higher in the elderly compared to young people.<sup>22</sup> The risk of pneumonia increases with advancing age in the presence of various conditions such as increased comorbid conditions (COPD, cardiovascular, endocrinologic, neurologic diseases), impaired swallowing function, repeated aspirations, impaired cognitive functions, inadequate and unbalanced nutrition, and immunosuppressive treatment.<sup>8,22</sup> In our study, pneumonia was the third most frequently diagnosed disease in patients n:133; (13.4%). Neurology is another department where ILC is most frequently requested. The risk of pulmonary infection and pulmonary embolism increases in the neurology patient group due to long-term immobility, senility, high risk of aspiration, and long hospitalizations, and GHK is required due to respiratory symptoms.<sup>20</sup> In the studies of Öztürk et al.,<sup>13</sup> Annakkaya et al.<sup>12</sup> and Aslan et al.,<sup>14</sup> the rates of consultation requested from neurology were found to be 10%, 4.9% and 9%, respectively. In our study, 57 (5.8%) consultations were requested from the neurology service and 20 (2.0%) from the neurology intensive care unit.

## CONCLUSION

Chest diseases is the department most frequently requested for consultation by other services. However, there is no standardized approach for consultations. It would be appropriate to develop standardized forms for consultations, to keep proper records, and to take complete examinations and anamnesis. In addition, it is thought that requesting a consultation after a good evaluation by the relevant clinic before requesting a GHK will be of great clinical benefit and will reduce labor loss.

## ETHICAL DECLARATIONS

### Ethics Committee Approval

The study was carried out with the permission of Ethical Committee of Faculty of Medicine, Ankara University (Date:21.09.2023, Decision No: 22499618).

### Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

### Referee Evaluation Process

Externally peer-reviewed.

### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

### Financial Disclosure

The authors declared that this study has received no financial support.

### Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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# Exploring the competence of artificial intelligence programs in the field of oculofacial plastic and orbital surgery

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## ABSTRACT

**Aims:** It aims to evaluate the knowledge level of ChatGPT, Bing, and Bard artificial intelligence chatbots developed based on large language models (LLM) about oculofacial plastic surgery and to investigate the presence of superiority over each other.

**Methods:** Twenty-nine questions that tested knowledge about oculofacial plastic and orbital surgery were taken from the study questions section of the American Academy and Ophthalmology 2022-2023 Basic and Clinical Science Course Oculofacial Plastic and Orbital Surgery. The questions were asked to ChatGPT, Bing, and Bard programs, which are current artificial intelligence chatbots. The questions were classified as either correct or incorrect.

**Results:** ChatGPT gave 44.8% correct answers, Bing 48.3% correct answers, and Bard 58.6% correct answers to 29 questions about artificial intelligence chatbots. No statistical difference was observed between the rates of correct and incorrect answers given by 3 the intelligence programs ( $p=0.609$ , Pearson's chi-squared test).

**Conclusion:** The use of artificial intelligence to access information regarding oculofacial plastic and orbital surgery may provide limited benefits. Care should be taken in terms of accuracy and timeliness when evaluating the results of artificial intelligence programs.

**Keywords:** Bard, Bing, ChatGPT, oculofacial plastic surgery, orbital surgery

## INTRODUCTION

Artificial intelligence is a sub-branch of computer science that aims to provide answers similarly by imitating the human mind.<sup>1</sup> The implementation of the first studies dates back to the early 1970s.<sup>2</sup> Although it has a wide variety of features, examples can be given to recognizing images, generating ideas to solve problems, and comprehending what is spoken.<sup>3</sup> Large language models (LLM), a sub-branch of artificial intelligence applications that can perceive inputted information, evaluate and summarize them, predict a wide variety of meaning possibilities, evaluate all these in a broad context, and draw conclusions as a result.<sup>4</sup> The development of LLMs has revolutionized the development of artificial intelligence chatbots.<sup>5</sup> Examples of these developed chatbots as Chat generative pre-trained transformer (ChatGPT) produced by OpenAI, Bing produced by Microsoft, and Bard artificial intelligence chatbots produced by Google AI.

With these recent developments, artificial intelligence programs have led to the formation of a new academic environment that has gained features such as synthesizing, processing, and analyzing data. Considering these advantages, interest in artificial intelligence programs in

medical sciences has also increased.<sup>6</sup> They were even used in the writing of some articles and they were mentioned as the author.<sup>7,8</sup>

Our aim in this study is to evaluate the knowledge level of ChatGPT, Bing, and Bard artificial intelligence programs, which are offered free of charge by 3 different manufacturers with the increasing developments in artificial intelligence, in the field of oculofacial plastic and orbital surgery and to investigate the presence of superiority to each other.

## METHODS

All 29 questions testing knowledge about oculofacial plastic and orbital surgery from the study questions section of the American Academy of Ophthalmology 2022-2023 Basic and Clinical Science Course Oculofacial Plastic and Orbital Surgery book were included in the study.<sup>9</sup> The questions were asked separately on 15 July 2023 to ChatGPT GPT-3.5 (OpenAI; San Francisco, CA), Bing (Microsoft, Redmond, Washington), and Bard (by Google) artificial intelligence chatbots, which can be used for free. First, we ask multiple-choice questions. Tell me the correct answer option."

command was given. After each question, the chat session was restarted to exclude memory retention features of artificial intelligence programs. The answers to the questions were compared with the answer keys and categorized as correct or incorrect. Additionally, common answers to the same question were determined and grouped as correct or incorrect.

### Statistical Analysis

Statistical Package for the Social Sciences version 23 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis of the data. The percentages were calculated using descriptive statistics. Pearson chi-square and Yates chi-square tests were used for the statistical comparison of independent nominal values. Differences were considered statistically significant at  $p < 0.05$ .

## RESULTS

Twenty-nine questions about oculofacial plastic and orbital surgery were asked in all three artificial intelligence programs. The ChatGPT artificial intelligence program gave correct answers to 13 (44.8%) questions and incorrect answers to 15 (51.7%) questions. ChatGPT replied to one of the questions asked, "As of the last update in September 2021, I could not find a definitive answer to this question." The Bing artificial intelligence program gave correct answers to 14 (48.3%) questions and incorrect answers to 15 (51.7%) questions. On the other hand, the Bard artificial intelligence program gave correct answers to 17 (58.6%) questions and incorrect answers to 12 (41.4%). The number of questions for which all 3 programs gave the same answers was 16 (55.2%). These programs gave correct answers to 9 (56.3%) of the questions and incorrect answers to 7 (43.8%) (Table).

**Table. The success of artificial intelligence chatbots on questions related to oculofacial plastic and orbital surgery**

Answers (n)	ChatGPT	Bing	Bard
Correct	13 (44.8%)	14 (48.3%)	17 (58.6%)
Incorrect	15 (51.7%)	15 (51.7%)	12 (41.4%)
Same answers (n)	16 (55.2%)		
Correct	9 (56.3%)		
Incorrect	7 (43.8%)		

There was no statistically significant difference between the correct and incorrect answers given by ChatGPT, Bing, and Bard artificial intelligence chatbots ( $p = 0.609$ , Pearson chi-square test). There was no statistical difference between the correct and incorrect response rates of the ChatGPT and Bing chatbots ( $p = 1.0$ , Yates chi-squared test). There was no statistically significant difference between the correct and incorrect response rates of the ChatGPT and Bard chatbots ( $p = 0.512$ , Yates chi-squared test). There was no statistically significant difference between the correct and incorrect response rates of the Bing chatbot and the Bard chatbot ( $p = 0.599$ , Yates chi-square test).

## DISCUSSION

ChatGPT, developed based on LLM, is a program that has been processed with 175 billion parameters and aims to produce answers that are similar to the human mindset. Thanks to this complex structure, it has taken a step forward among

similar programs.<sup>10</sup> ChatGPT; thanks to its various features such as making a personalized learning plan, performing translations, and helping research, has also found many uses in the field of medicine.<sup>11</sup> In general, ChatGPT is a useful artificial intelligence program for accessing information quickly and reliably. These benefits continue in the medical field. Its use in obtaining information about various diseases, making differential diagnoses, and obtaining information about a wide variety of treatment modalities is an example of its use in the medical field. In addition, being able to examine and analyze medical literature and find summaries of texts are examples of its benefits to medical researcher.<sup>12</sup> Considering all these advantages, it appeals to a wide audience from medical students to a wide range of health professionals, and has various benefits.<sup>13</sup> In addition to ChatGPT, LLM-based Bing and Bard artificial intelligence programs, which were introduced in 2023, also contain similar features. We believe that the advantage of these LLM-based artificial intelligence chatbots in accessing information quickly and reliably can contribute to the learning of diseases and treatment methods related to oculofacial plastic and orbital surgery. In addition, we believe that these programs can help people who are trained and specialized in oculofacial plastic and orbital surgery to save and use time more efficiently. In addition to the various advantages mentioned above, these programs have some disadvantages. Examples of these are the sources referenced for medical information, free online websites on the Internet, limited access to paid articles, and ChatGPT's last update in September 2021.<sup>10,14</sup> Considering all these, it comes to mind that artificial intelligence programs may have problems accessing up-to-date information in constantly renewing medical fields and may raise doubts about the accuracy of the information. Although its wide range of benefits is reassuring for use in the medical field, it is important to test its clinical usefulness and examine its performance.<sup>15,16</sup> We also conducted this study; we designed it to test the performance of artificial intelligence programs on whether they can be used as a resource to access accurate information about oculofacial plastic and orbital surgery under a wide variety of advantages and disadvantages.

In recent years, various studies have answered medical questions and examined their correct and incorrect response rates. Examples include the study in PubMed, which states that the accuracy rate of the models that test the answers to yes or no questions is 68.1%, and a study that examines a dataset of 12,723 questions and states that the accuracy rate is 36.7%.<sup>17,18</sup> With the recent developments in artificial intelligence, the use of artificial intelligence programs such as ChatGPT, Bing, and Bard, which can detect and respond to more complex questions, in answering medical questions has come to the fore. For this purpose, ChatGPT's success in answering the questions in the USMLE has been tested and it has been shown that it can provide more than 50% correct answers.<sup>19</sup> In a study examining the reliability of these artificial intelligence programs in answering ophthalmology-related questions, questions were asked to ChatGPT and Bing artificial intelligence chatbots. It was stated that artificial intelligence programs gave correct answers to the questions at a rate of 58.8% and 71.2%, respectively.<sup>14</sup> We asked 29 questions to the ChatGPT, Bing, and Bard artificial intelligence programs that test the knowledge about oculofacial plastic and orbital surgery, and we found the correct answer rates to be 44.8%, 48.3%, and 58.6%, respectively. ChatGPT's answer

to one question, "As of my last update in September 2021, I could not find a definitive answer to this question." supported our suspicion that this artificial intelligence program may be far from up-to-date information and will have limited effects on accessing the right answer. This rate of all 3 artificial intelligence programs answering the questions correctly may be related to the limited access to current information. Differences in the information tested by the questions and the structure of the questions may have reduced the success of artificial intelligence chatbots. The questions we tested were only related to a specialized field and were taken from a current book. Both the questioning of current information and the existence of a single specialized field may have caused the difference between success rates and other studies. When we evaluated the artificial intelligence chatbots in our study among themselves, although there was no statistically significant difference between the three programs, it was observed that Bing and Bard artificial intelligence programs, which came into use in 2023, had a higher correct answer rate. We think that this situation may be related to the fact that Bing and Bard chatbots can provide access to more up-to-date information.

### Limitations

The limitations of the study are that artificial intelligence programs are not specific to medicine, there is no intervention in the operational steps, there is limited access to paid sites, and there is a limitation of ChatGPT in accessing data from 2022 and beyond.

### CONCLUSION

As a result, to the best of our knowledge, our study is the first to test the knowledge levels of free artificial intelligence programs released by three different manufacturers based on LLM about oculo-facial plastic and orbital surgery and investigate the existence of superiority to each other. Although more recently released artificial intelligence programs, such as Bing and Bard, have higher accuracy in answering questions, the information provided may make a limited contribution to providing users with access to correct information. Care should always be taken regarding the reliability and accuracy of the information provided by artificial intelligence programs.

### ETHICAL DECLARATIONS

#### Ethics Committee Approval

Since our article does not contain human or animal subjects, it does not require an ethics committee approval.

#### Informed Consent

Since our article does not contain human or animal subjects, it does not require an informed consent.

#### Referee Evaluation Process

Externally peer-reviewed.

#### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

### Financial Disclosure

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### Author Contributions

All of the authors declare that have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

### Data availability statement

All data generated or analyzed during the present study are included in this published article.

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# Efficacy of ferric carboxymaltose therapy in celiac patients

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## ABSTRACT

**Aims:** Iron deficiency anemia (IDA) is the most common cause of anemia worldwide. IDA can be caused by reduced iron intake, impaired iron absorption or losses. Celiac disease can cause iron malabsorption by decreasing the surface absorption area in the duodenum and consequently can cause IDA. Oral or intravenous iron preparations are used in the treatment of IDA. In this study, we wanted to investigate the efficacy of ferric carboxymaltose (FCM) in celiac patients with RIA.

**Methods:** Twenty-three patients who were followed up in the gastroenterology outpatient clinic of İnönü University Medical Faculty Hospital Turgut Özal Medical Center with the diagnosis of celiac disease and who received FCM were included in the study. The hemogram, ferritin, iron and iron binding levels of the patients were retrospectively screened through the hospital medical record system.

**Results:** Of the 23 patients included in the study, 3 (13.05%) were male and 20 (86.95%) were female. Hemoglobin concentration, iron and iron binding capacity before and after treatment showed a significant increase in all parameters after treatment. Ferritin value increased, although not significantly.

**Conclusion:** In our study, we found that FCM is an effective and safe treatment modality in the treatment of IDA in celiac patients

**Keywords:** Anemia, celiac disease, ferric carboxymaltose

## INTRODUCTION

Iron deficiency anemia (IDA) is the most common cause of anemia worldwide, affecting about one third of the population. IDA leads to a hypochromic microcytic anemia. Causes of IDA can include reduced iron intake or impaired absorption in the gastrointestinal (GI) tract, losses (such as chronic GI and menstrual bleeding), or increased need, such as during puberty and pregnancy.<sup>1,2</sup> Celiac disease (CD) is one of the unexplained causes of IDA. CD is an immune-mediated disease in which iron malabsorption and consequently ADEs develop due to a decrease in the surface absorption area in the duodenum due to an inflammatory process in the intestine.<sup>1</sup>

Oral iron therapy (OIT) is usually the first line treatment for anemia due to definite iron deficiency. However, a significant proportion of patients do not respond to OIT. This is because some patients do not comply with the treatment due to GI side effects. In addition, OIT may not be appropriate in cases of poor absorption of iron due to GI disorders and in cases of severe IDA where rapid response with OIT is not achieved.<sup>3</sup> In such cases, IV iron administration has been found to be more effective in correcting IDA without significant safety concerns.<sup>1</sup>

In this study, we aimed to present data on the efficacy and safety of ferric carboxymaltose (FCM) treatment in patients with CD presenting with IDA.

## METHODS

Between January 2009 and December 2023, 23 patients who were followed up in the Gastroenterology Outpatient Clinic of İnönü University Medical Faculty Hospital Turgut Özal Medical Center with the diagnosis of CD and who received FCM were included in the study. Ethical approval was obtained from İnönü University Scientific Researches and Publication Ethics Committee for the study (Date: 02.04.2024 Decision No: 2024/5716). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The hemogram values, iron, iron binding and ferritin levels of the patients were retrospectively screened through the hospital medical record system. None of the patients received oral iron therapy in the last 6 months before FCM treatment.

The diagnosis of CD was accepted as positive if the titer of tissue transglutaminase IgA antibody in serum samples was >18 AU/ml. Upper gastrointestinal endoscopy was performed in patients with positive serologic tests and duodenal biopsy was performed. Marsh-Oberhuber criteria were used for histopathologic staging.

Pre-treatment values of the patients and control values after FCM intake were obtained. Patients were administered 500

mg / 10 ml of FCM in 100 cc isotonic water by infusion over 15 minutes, 2 times with an interval of 1 week. Statistical evaluation was performed using SPSS 22 (Statistical Package for the Social Sciences) version. Student t test was used and  $p < 0.05$  was considered significant.

## RESULTS

Of the 23 patients included in the study, 3 (13.05%) were male and 20 (86.95%) were female. The median age of the patients was 33.7 years (21-50 years). When the distribution of median hemoglobin concentration, iron and iron binding capacity before and after treatment was analyzed, a significant increase was observed in all parameters after treatment ( $p < 0.005$ ). Ferritin level increased, although not significantly. The distribution of hemoglobin concentration, ferritin level, iron and iron binding capacity before and after treatment is shown in Table. No serious side effects were observed in any patient receiving intravenous FCM treatment.

Table. Intra venous ferric carboxymaltose therapy

	Pre-treatment (mean)	Post-treatment (mean)	p*
Hemoglobin	10	12.3	<0.001
Ferritin	15.4	29.2	0.22
Iron	29.5	89.8	<0.05
IBC	387.6	298.3	<0.05

IBC; iron binding capacity

## DISCUSSION

Anemia as defined by the World Health Organization (WHO), hemoglobin (Hb) below 13 g/dl in men over 15 years of age, below 12 g/dL in women over 15 years of age and not pregnant, and below 11 g/dL in pregnant women. The degree of IDA can be determined by serum ferritin and transferrin saturation. In patients without evidence of inflammation, a ferritin level of less than 30 µg/liter or a transferrin saturation of less than 16% is required for the diagnosis of IDA.<sup>4,5</sup>

FCM is a novel iron complex consisting of a ferric hydroxide core and a carbohydrate shell that stabilizes it. FCM allows controlled delivery of iron to the cells of the reticuloendothelial system and the release of large amounts of ionic iron in serum minimizes the risk. The incidence of adverse events in patients receiving intravenous FCM was similar to that in patients receiving oral ferrous sulfate, with a lower rate of adverse events compared to iron sucrose recipients.<sup>6</sup>

FCM has been approved for use in patients with iron deficiency who do not respond well to oral iron therapy, have intolerance to oral iron preparations, or are on dialysis due to end-stage renal failure, rather than as first-line treatment.<sup>5</sup> In a study by Raquel Ballester-Clau et al.<sup>8</sup> involving 34 patients with liver cirrhosis and GI bleeding, it was observed that early FCM treatment achieved optimal serum Hb levels in patients. It was thought that FCM could be included in first-line treatment.<sup>7</sup> FCM was found to be effective in randomized controlled trials with diseases such as inflammatory bowel disease, chronic kidney disease with or without hemodialysis, chronic heart failure, uterine bleeding, and postpartum anemia.

IDA is the only abnormality observed in approximately 40% of CD. The cause is inflammation of the duodenal mucosa leading to villous atrophy. However, some CD continue to have IDA despite a gluten-free diet and normalization of villous atrophy and are resistant to oral iron supplementation. These patients require periodic intravenous iron administration.<sup>9</sup>

In a study involving 184 individuals, 47 of whom were in the control group and 137 of whom were iron deficiency patients. It was observed that 45 of 137 patients did not respond to iron treatment. Serology was positive for CD in 19 (10.3%) of 184 patients. Of these patients, 13 were treatment-resistant patients, 5 were patients who recovered with treatment and 1 was a control group. Celiac serology positivity was significantly higher in the treatment-resistant group compared to the other two groups.<sup>10</sup> Since the incidence of CD is higher in IDA patients compared to the normal population, serum screening tests for CD should be performed in these patients.

The main treatment for CD is a gluten-free diet. The CD diet may improve mild forms of IDA. Differences of opinion persist regarding oral or intravenous treatment for iron supplementation. Ferrous sulfate is the most widely used treatment because it is inexpensive, easy to administer and has no risk of life-threatening adverse events. Gastrointestinal side effects in 50% of these patients limit its use. With a gluten-free diet in CD, healing of intestinal lesions is delayed and therefore iron stores are replenished later than in normal individuals. In recent years, IV iron agents such as Fe-sucrose and Fe-carboxymaltose have been developed and are under investigation.<sup>11</sup> In our clinic, we observed that anemia improved significantly in patients who received FCM.

Nausea, headache, abdominal pain, diarrhea, hypophosphatemia and rarely hypersensitivity reactions may occur after FCM intake.<sup>12</sup> No serious side effects were observed in any of our patients.

The limitations of this study were that it was retrospective and was conducted in a small group of patients.

## CONCLUSION

In this study, we examined hemoglobin, iron, iron binding and ferritin values to evaluate the effectiveness of FCM treatment in CD with iron deficiency. We found that FCM treatment is effective and safe in correcting these parameters. However, we think that prospective studies in larger patient populations are needed.

## ETHICAL DECLARATIONS

### Ethics Committee Approval

Ethical approval was obtained from İnönü University Scientific Researches and Publication Ethics Committee for the study (Date: 02.04.2024 Decision No: 2024/5716).

### Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

### Referee Evaluation Process

Externally peer-reviewed.



### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

### Financial Disclosure

The authors declared that this study has received no financial support.

### Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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# Approach to restless leg syndrome in hemodialysis patients

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## ABSTRACT

Restless legs syndrome (RLS) is an uncomfortable urge to move the legs while the person is at rest. This movement disorder is one of the problems that may develop in the follow-up of hemodialysis patients. It is important to recognize and treat these problems because they are closely related to mortality and morbidity. It is estimated that RLS symptoms occur in 3% of the adult population worldwide and in approximately 27% of hemodialysis patients. Although the pathophysiology of the disease and its relationship with its high prevalence in dialysis patients have not yet been clearly elucidated, it is predicted that pathologies such as central dopamine metabolism disorders, iron deficiency and uremia may underlie the disease. There are some pharmacological and non-pharmacological treatment methods developed based on available data. Current data in the literature regarding the effectiveness and superiority of these treatments are insufficient to clarify the treatment approach. Studies on the subject continue and the unknowns in treatment and pathophysiology are being clarified day by day.

**Keywords:** Restless legs syndrome, Willis-Ekbom disease, hemodialysis

## INTRODUCTION

Dialysis patients may face some physical, psychological and social problems due to many reasons such as having a chronic disease, the need for continuous treatment, and the feeling of dependence on treatment. It is predictable that quality of life is lower in these patients compared to the general population.<sup>1</sup> In addition, quality of life in dialysis patients has been found to be closely associated with mortality and morbidity. Because of this close relationship, it is important to recognize and treat problems that may develop during follow-up.<sup>2</sup> Restless leg syndrome (RLS) is one of the conditions that affect the health and quality of life of these patients. RLS also known as Willis-Ekbom disease, is a disturbing urge to move the legs while resting, sitting or sleeping that disrupts sleep.<sup>3,4</sup> Hemodialysis patients constitute a large group of the population likely to be affected by RLS due to severe uremia.<sup>3</sup> RLS symptoms are estimated to occur in 3% of the adult population worldwide.<sup>5</sup> When looking at the prevalence of these symptoms among hemodialysis patients, different prevalence results are found in studies.<sup>6</sup>

Although there are variable results in the literature regarding the prevalence of RLS in hemodialysis patients, it is noteworthy that RLS affects a substantial majority of these patients. Furthermore, studies show that despite its high prevalence, RLS, along with other symptoms that affect patients' lives, is under-recognized and therefore under-treated.<sup>7</sup> The presentation of RLS in these patients is highly variable and symptoms are intermittent and fluctuating,

which is predicted to lead to delayed diagnosis.<sup>3</sup> RLS may affect sleep quality and increase the risk of cardiovascular disease in hemodialysis patients.<sup>8</sup> Furthermore, symptom intensity is linked to poor sleep quality, impaired physical functioning and lifestyle standards, and increased mortality risk.<sup>9</sup> Considering all these, it is important to recognize and treat RLS in patients receiving hemodialysis treatment.

## DEFINITION

RLS, a neurological sensory-motor disorder that often profoundly affects sleep and quality of life, is often influenced by genetic, environmental and medical factors in the course of the disease. The frequency of symptoms ranges from once a month to every day, and the severity varies considerably from annoying to disabling. The diagnosis of RLS is made by identifying symptom patterns that meet the five basic criteria mentioned in [Table 1](#). Hemodialysis patients are also diagnosed according to these criteria.<sup>10</sup> All five basic criteria must be met for the diagnosis of RLS. In addition to the diagnostic criteria, the International Restless Legs Syndrome Study Group has developed a single standardized question with a sensitivity of 100% and specificity of 96.8% for rapid screening of the disease: 'In the evening or at night when you sleep, do you have unpleasant, restless sensations in your legs? Because of its high sensitivity and specificity, this question can be used for screening purposes in large groups of patients, especially in hemodialysis patients. However,

the final diagnosis should always be based on diagnostic criteria. In addition, differential diagnoses such as myalgia, leg cramps, arthritis, leg shaking habit, anxiety, myopathy should be kept in mind during the diagnostic phase.<sup>10,11</sup>

**Table 1. International Restless Leg Syndrome Study Group diagnostic criteria<sup>10</sup>**

The need to move the legs, which is often, but not always, accompanied by or caused by uncomfortable and unpleasant sensations in the legs
These symptoms start or worsen at rest, such as lying or sitting.
These symptoms partially or completely resolve during movement, such as walking or stretching, for as long as the activity continues.
These symptoms occur only in the evening or at night, or are significantly more severe at these times than during the day.
The above symptoms cannot be explained in isolation by symptoms related to another medical or behavioral condition (e.g. leg cramps, positional discomfort, myalgia, venous stasis, leg edema, arthritis, foot shaking)

In RLS, it is very important to be able to numerically determine the symptom that bothers the patient the most and the severity of the disease. A number of scales have been developed to objectively measure the patient's level of discomfort and response to treatment. Developed in 2003 by the International RLS Study Group, the disease severity scale is considered the gold standard.

## PATHOPHYSIOLOGY AND ETIOLOGY

Although the pathophysiology of RLS is still unknown, iron and dopamine metabolism in the brain are thought to play an important role in the development of the disease.<sup>11</sup> Some genetic variations have also been found to be a risk factor for the development of the disease. When the disease is analyzed etiologically, it is basically divided into primary and secondary. Primary RLS is mostly thought to be due to cerebral iron deficiency, dopamine system dysfunction and increased glutamate levels. Secondary causes include end-stage renal disease, uremia, iron deficiency, drugs and pregnancy.<sup>12</sup>

### Pathophysiology and Possible Risk Factors in Hemodialysis Patients

The pathophysiology in hemodialysis patients has not yet been fully elucidated. Since uremia is one of the secondary causes of RLS, it is assumed that RLS is common in end-stage renal disease patients receiving hemodialysis. It is also known that bone-mineral metabolism disorders are encountered in patients with chronic kidney disease. In some studies on the pathophysiology in these patients, hyperphosphatemia was independently associated with the presence of RLS.<sup>13,14</sup> In another study, no significant difference was found between the group with and without RLS symptoms when serum PTH and phosphorus levels were analyzed.<sup>15</sup> Some studies have found that hyperparathyroidism, hyperphosphatemia, and vitamin D deficiency are associated with the incidence and severity of RLS in hemodialysis patients, suggesting that bone metabolism disorder may be associated with RLS.<sup>16</sup>

In terms of the role of genetics in these patients, a study evaluating the association of MEIS1 and BTBD9 polymorphisms with RLS showed significant results in some populations.<sup>17</sup> Another study revealed that hemodialysis patients with RLS symptoms had a significantly longer hemodialysis duration and higher cardiothoracic ratio, as

well as higher levels of inflammatory markers and lower transferrin saturations compared to those without RLS symptoms.<sup>18</sup> Uremia-induced pruritus, iron deficiency anemia, and inadequate response to erythropoietin alpha were also found to be associated with RLS in these patients.<sup>3,19</sup> Considering these results, chronic inflammatory process and oxidative stress may also play a role in the development of the disease. In addition, a significant correlation between serum hemoglobin level and the development of RLS has been found in many studies in these patients.<sup>15</sup> It should be kept in mind that anemia, which is frequently encountered in patients with chronic kidney disease, may also be a risk factor for the development of RLS. In terms of iron deficiency, although many studies have found a significant correlation with RLS, the relationship between ferritin and RLS is doubtful since serum ferritin level is an acute phase reactant. When the relationship between serum hepsidin levels and RLS is analyzed, it can be said that significant results were found.<sup>20</sup>

When the relationship between the severity of the disease and some laboratory parameters in hemodialysis patients with RLS symptoms was examined, iron, total iron binding capacity, calcium and transferrin saturation, as well as dialysis duration were found to be associated with the severity of the disease.<sup>21</sup> Among patients receiving hemodialysis, female gender and alcohol use were reported to be risk factors for the development of RLS.<sup>22</sup> Several other studies have also shown that being female was significantly associated with RLS in patients receiving hemodialysis.<sup>23-25</sup> While some studies found a significant relationship between the duration of hemodialysis treatment and RLS,<sup>8,15,26</sup> This relationship was not found in some studies.<sup>23,25</sup> In this group of patients who are likely to encounter psychological problems, there are studies in which anxiety and RLS were found to be related.<sup>13</sup>

Regarding the effect of dialysis modality, it was found that receiving hemodialysis or peritoneal dialysis treatment did not affect the development of RLS or the severity of the disease in patients with RLS.<sup>27</sup>

## EPIDEMIOLOGY

When the studies are analyzed, we come across different results regarding the prevalence. Prevalence varies according to several factors such as gender, sample size and geographical region.<sup>6</sup> In 2024, as a result of a meta-analysis evaluating 97 studies conducted in 21 different countries, the global pooled prevalence of RLS in hemodialysis patients was calculated as 27.2%. In the same study, the prevalence was found to be higher in women compared to men.<sup>6</sup>

## TREATMENT APPROACHES

Treatment methods can be roughly classified as pharmacologic and non-pharmacologic methods. These treatment approaches are summarized in Table 2. Additional comorbidities in patients should also be considered when evaluating treatment options.<sup>28</sup> Uncertainties in the pathophysiology of the disease do not allow for a clear treatment approach. Moreover, controlled studies on long-term treatment responses and adverse events are limited.<sup>29</sup> As such, the evidence in the literature for the treatment of RLS patients receiving hemodialysis is much more limited. In addition, drugs used in the treatment of primary RLS

may have side effects when used directly in the treatment of RLS patients receiving hemodialysis. According to 2016 guidelines published by the American Academy of Neurology, clinicians are advised to consider prescribing vitamin C and E supplements (Level B evidence) and ropinirole, levodopa or exercise (Level C evidence) for the treatment of RLS in hemodialysis patients. It has been stated that there is insufficient evidence to support or refute the use of gabapentin or IV iron in the treatment of these patients, and insufficient evidence to support or refute the superiority of gabapentin or levodopa over one another.<sup>12</sup>

**Table 2. Treatment approaches for RLS in patients receiving hemodialysis treatment**

Pharmacological therapies	Non-pharmacological therapies
Dopamine agonists	Cold dialysate
Gabapentins	Massage
Vitamins C and E	Exercise

RLS: Restless legs syndrome

### Pharmacological Treatment

**Dopamine Agonists:** Non-ergot dopamine agonists such as rotigotine, ropinirole and pramipexole are used in the treatment of primary RLS. The number of studies on the use of these drugs in the treatment of hemodialysis-related RLS is limited. In a prospective multicenter study, it was observed that rotigotine improved clinical symptoms of RLS and quality of life in hemodialysis patients.<sup>30</sup> An experiment on mice with rotigotine using serum from dialysis patients suggested that it may be effective in the treatment of RLS in hemodialysis patients.<sup>31</sup> Ropinirole has been shown to improve RLS symptoms, sleep duration and quality of life in dialysis patients and also shows fewer side effects.<sup>32</sup> Pramipexole has a large volume of distribution in the blood and therefore cannot be easily cleared from the blood in hemodialysis patients. In the light of this information, rotigotine or ropirinol may be considered instead of pramipexole as a dopamine agonist in the treatment of hemodialysis patients with RLS. It has been found that dopamine receptor agonists may be associated with various adverse effects such as nausea in the short term and re-exacerbation of symptoms in long-term use.<sup>33,34</sup> Short-term side effects disappear after the drug is discontinued. Due to these side effects that may occur during pharmacologic treatment, non-pharmacologic treatments play an important role in the management of the disease. Due to the potential effect of central dopamine metabolism disorders in the pathophysiology, dopamine receptor agonists may be effective in the treatment of the disease through this pathway.

**Gabapentins:** The other group of pharmacologic agents used in the treatment of RLS are gabapentins. There is insufficient evidence to support or refute the use of gabapentin in the treatment of dialysis-induced RLS.<sup>12</sup> A meta-analysis in 2022 concluded that gabapentins are the most potent pharmacological agent in the treatment of RLS due to hemodialysis.<sup>35</sup>

**Vitamin C and E:** According to the American Academy of Neurology guidelines, the first choice pharmacologic agent recommended in patients with RLS secondary to hemodialysis is vitamins C and E.<sup>12</sup> Supplementation of these vitamins can be given singly or in combination. Following these recommendations, a meta-analysis conducted in 2021 concluded that vitamin C, followed by ropirinol, may be

the most effective treatment in these patients in the light of available evidence.<sup>35</sup> Considering the antioxidant effects of these vitamins, vitamin E and C can be considered as a safe choice among pharmacological agents in people with RLS symptoms due to hemodialysis. In addition, depression and RLS are closely associated with insomnia in these patients. In addition to treatments for RLS, treatment of depression and insomnia may be useful in improving quality of life in hemodialysis patients.<sup>36</sup>

### Non-pharmacological Methods

**Cold dialysate:** Dialysate is the solution used to stabilize the blood levels of patients receiving hemodialysis. The dialysate temperature is traditionally set at 37°C to maintain isothermia (between 36.5°C-36.9°C). Cold dialysis is performed by lowering the dialysate temperature to 35°C-36°C or 0.5°C below the resting body core temperature. Cold dialysate has the advantage of being one of the easily modifiable treatment options for patients with RLS on hemodialysis, as well as reducing the risk of intradialytic hypotension.<sup>37</sup> In 2022, dopamine agonist, gabapentin, iron, vitamin C, vitamin E, cold dialysate, intradialytic stretching exercise, intradialytic aerobic exercise, intradialytic aerobic exercise and dopamine agonist, aromatherapy massage, reflexology, acupuncture treatment, As a result of a meta-analysis in which 24 studies were evaluated to compare the effectiveness between neuromuscular electrical stimulation treatments, it was concluded that cold dialysate was the most effective treatment in reducing the severity of RLS and gabapentin was the most powerful pharmacological treatment. It has been suggested that there is limited evidence on the effectiveness of massage therapy, which can be considered among other treatment modalities.<sup>35</sup>

**Massage:** A meta-analysis conducted in 2022 showed that massage therapy reduced the symptoms and severity of RLS due to hemodialysis.<sup>34</sup> In addition, in this study, the effect of massage therapy with lavender oil was examined and it was concluded that lavender oil may also be effective in the treatment of RLS due to its effect on relieving muscle pain and strengthening immunity. The minimal side effect profile is also an advantage of this treatment option. Some studies have suggested that massage therapy has the potential to stimulate the nervous system by accelerating dopamine secretion and thus may be effective in the treatment of RLS.<sup>38</sup>

**Exercise:** Exercise is one of the non-pharmacologic treatment options in hemodialysis patients. Aerobic exercise or intradialytic stretching exercises have been shown to alleviate pain and improve sleep quality in RLS. In one study, a 6-month exercise training regimen was found to be as effective as 6-month low-dose dopamine agonist treatment in reducing RLS symptoms and improving depression score in uremic patients.<sup>39</sup>

### CONCLUSION

Patients receiving hemodialysis treatment face various problems during the disease process. One of these problems is RLS. Despite its high prevalence, RLS in hemodialysis patients is recognized late and therefore treated late in clinical practice. There are pharmacologic and non-pharmacologic treatment approaches for RLS in dialysis patients. Although there are studies on this subject in the literature, the available

data do not allow an optimal approach and treatment route to be established. There is a need for more studies in this patient group in terms of approach to RLS and development of effective treatment methods.

## ETHICAL DECLARATIONS

### Referee Evaluation Process

Externally peer-reviewed.

### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

### Financial Disclosure

The authors declared that this study has received no financial support.

### Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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# Treatment of recurrent pulmonary thromboembolism with echosonic endovascular system

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## ABSTRACT

Venous thromboembolism is a collective term that describes two diseases, pulmonary thromboembolism (PE) and deep vein thrombosis, with or without symptoms but often accompanying each other. PE develops in most cases due to thrombus formation in the deep veins of the lower extremities and migrates to the pulmonary artery and/or its branches. It is a preventable disease with high mortality and morbidity and includes diagnostic difficulties. Recurrence may occur despite treatment in 5-23% of PE cases. Patients may apply to the hospital with symptoms such as unexplained dyspnea, stabbing or atypical chest pain, hemoptysis, and syncope. We aimed to present the patient who had chronic deep vein thrombosis (DVT) and was frequently hospitalized due to recurrent massive PE. In our case, disease status requires catheter thrombolytic therapies two times in three months.

**Keywords:** Venous thromboembolism, massive pulmonary thromboembolism, echosonic endovascular system

## INTRODUCTION

Venous thromboembolism is a collective term that describes two diseases, pulmonary thromboembolism (PE) and deep vein thrombosis, with or without symptoms but often accompanying each other. PE develops in most cases due to thrombus formation in the deep veins of the lower extremities and migrates to the pulmonary artery and/or its branches.

The major risk factors are fracture in lower extremity, heart failure or atrial fibrillation/flutter, hospitalization due to (in the last 3 months), hip or knee replacement, major trauma, myocardial infarction in the last 3 months, previous VTE and, spinal cord injury. The medium risk factors are arthroscopic knee surgery, autoimmune diseases, blood transfusion, central venous catheter, intravenous catheters, chemotherapy, congestive heart failure or respiratory failure, erythropoiesis stimulating agents, hormone replacement therapy, in vitro fertilization, oral contraceptive therapy, postpartum treatment, infection (especially pneumonia, urinary tract infection and HIV), inflammatory bowel disease, cancer (risk is high in the presence of metastasis), paralytic stroke, superficial vein thrombosis, and thrombophilia. The weak risk factors are bed rest for more than three days, diabetes mellitus, arterial hypertension, sitting still for long periods of time (plane or car travel), advanced age, laparoscopic surgery (cholecystectomy), obesity, pregnancy, varicose veins, and venous catheters.

It is a preventable disease with high mortality and morbidity and includes diagnostic difficulties. Recurrence may occur despite treatment in 5-23% of PE cases.<sup>1</sup> Patients are typically admitted to the hospital with symptoms such as unexplained dyspnea, stabbing or atypical chest pain, hemoptysis, and syncope. We aimed to present the patient who had chronic deep vein thrombosis (DVT) and was frequently hospitalized due to recurrent massive PE. In our case, disease status requires catheter thrombolytic therapies two times in three months.

## CASE

A 44-year-old female patient was consulted to us by a gynecologist and obstetrician due to shortness of breath, stabbing chest pain and low oxygen saturation that developed after endometrium curettage biopsy. It was learned that she had known hyperthyroidism and chronic DVT. The patient developed a pulmonary embolism about a year ago and had a vascular surgery while a temporary vena cava filter was installed during the surgery. The patient was given on rivaroxaban 20 mg 1x1. The patient had stopped rivaroxaban treatment about 2 weeks ago due to vaginal bleeding. She had no history of additional pulmonary disease. She had never smoked. She had no known family history of cardiopulmonary disease. She had known no history of

malignancy in her family or herself. She is a housewife and had no jobs but the whole family is farmer and she contributes to the family business. There was no recurrent pregnancy loss. During physical examination, breathing sounds were normal on auscultation. While pulse oxymeter was 97% at rest, the saturation was 73% after a 6-minute exercise test. Respiratory rate was 26/min, pulse 102/min, blood pressure 110/70 mmHg. In arterial blood gas, pH: 7.38 pCO<sub>2</sub>: 33.7 pO<sub>2</sub>: 72.6. Sinus tachycardia was detected in electrocardiography. On echocardiography, the right heart chambers were evaluated as normal and systolic pulmonary arterial pressure (sPAP) was evaluated as 30 mmHg. Laboratory tests resulted in D-Dimer level of 3530 ng/ml. Renal function tests and infection parameters were normal. An iso-hyperechoic thrombus was observed within the vein lumen in lower extremity venous Doppler ultrasonography.

In the patient's computed tomography (CT) pulmonary angiography, a filling defect compatible with embolism was observed in the lobar and segmental branches of the right pulmonary artery (Figure 1-4). The patient was diagnosed with massive PE. Enoxaparin sodium 2x0.6 ml subcutaneous was given during hospitalization. The rheumatologic markers, tumor markers and genetic evaluation of thrombophilia panel were found to be normal. The patient, who showed a clear improvement after the treatment, was discharged by continuing the rivaroxaban 20 mg/day.



Figure 1. There was a massive thrombus in right main pulmonary artery



Figure 2. There was a massive thrombus in right main pulmonary artery but a recanalisation started distally

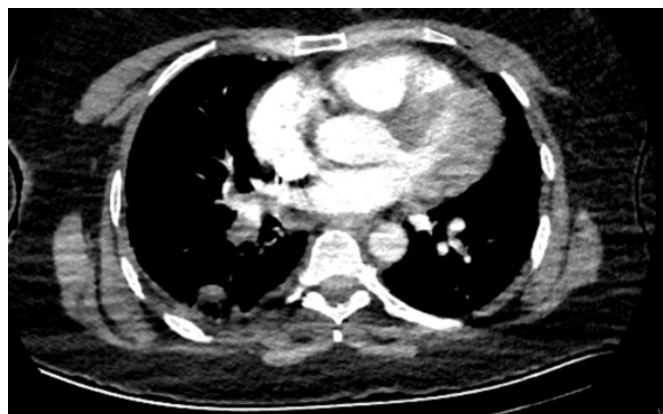


Figure 3. The right atrium and ventricle is dilated due to increased pulmonary hypertension

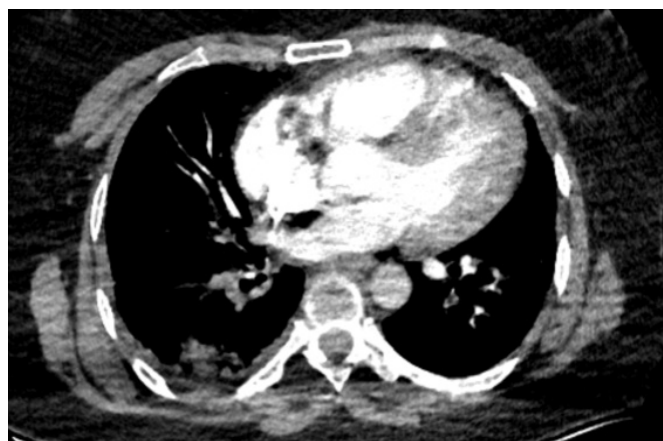


Figure 4. There is a necrosis area at the right lower lob posterior segment

The patient was admitted to the emergency room two months later with similar complaints and was hospitalized again. In current laboratory tests, D-Dimer was 1480 ng/ml and CT pulmonary angiography was reported as "hypo dense linear septations and incomplete thrombosis appearances compatible with right pulmonary artery, lower lobe segmental and left main pulmonary artery lower lobe segmentary-subsegmental chronic PE were observed." While the patient's treatment was continuing, the patient was consulted to cardiovascular surgery. The patients and relatives consent was taken for thrombolytic therapy. In the angiography unit, thrombolytic infusion was applied directly on the thrombus by reaching the pulmonary artery from the femoral vein with the Echosonic Endovascular System (EKOS) catheter, which is an ultrasound-accelerated thrombolytic treatment method, for a period of 24 to 48 hours (Figure 5-6). As thrombolytic therapy, alteplase 50 mg 1x1 was used intravenously for two days. After the EKOS procedure, heparin 25.000 IU was administered intravenously for two days in the intensive care unit. Oxygen saturation remained stable at rest. She discharged to the ward and after a successful 6-minute exercise test, she was discharged with medical therapy while sPAP was 30 mmHg.

The patient re-admitted to the emergency department 3 months later with severe shortness of breath and chest pain. The patient's current CT pulmonary angiography showed "hypodense thrombus was observed in the left main pulmonary artery, and a hypo dense thrombus area was also observed in the lower lobe branch of the right pulmonary artery. A wedge-shaped infarct area with its base resting on the pleura was observed in the laterobasal segment of the

lower lobe of the right lung. Similarly, there are infarct areas in the posterobasal segment of the upper lobe of the left lung, with a necrotic component and a base resting on the pleura." Echocardiography showed that the right heart chambers were wide, EF: 60%, systolic PAP: 80 mmHg. The patient was hospitalized, her treatment started with low molecular weight heparin (LMWH), and she was consulted again to cardiovascular surgery. It was decided to give the patient thrombolytic via catheter again, and the patient underwent an interventional procedure with the EKOS catheter again. The hemoglobin, hematocrit and platelet values before and after the procedure were normal. The thrombolytic procedure was successful again and the patient, whose "international normalized ratio" (INR) was monitored, was started on warfarin sodium 5 mg tablet and the dose was reduced and switched to 2.5 mg tablet. The follow-up of the patient continued without any problems, and systolic PAP decreased to 40 mmHg in the post-intervention echocardiography. The patient was taken to the pulmonary rehabilitation program at the hospital and discharged with full recovery. The patient's follow-up is still being carried out closely for chronic thromboembolic pulmonary hypertension (CTPH).



Figure 5. The catheterisation of right pulmonary artery

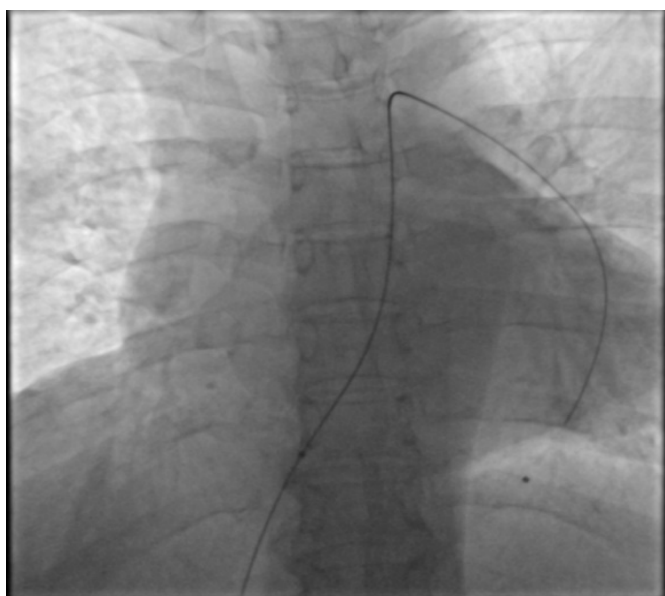


Figure 6. The catheterisation of right ventricle

## DISCUSSION

This case was a recurrent PE and threatened two times with thrombolytic therapy. The patient is a young woman and had no reason for thrombophilia. The genetic evaluation was also normal. There was not any provoked PE or VE. We searched the patient for any malignancy or infection and found nothing until today. The patient is relieved after the last thrombolytic therapy and she was given warfarin.

PE is a disease with high complications, morbidity and mortality. In cases of venous thromboembolism, recurrence may occur under treatment and after treatment is completed. Recurrence rates under treatment were varying between 0.6% and 2.5%. Especially in the first two years after venous thromboembolism (VE), the risk of recurrence is highest. Afterwards, the risk continues to decrease. VE recurrence increases the risk of mortality. Many risk factors have been identified that increase susceptibility to venous thromboembolism. The most frequently reported risk factors in studies are; previous history of VE, active cancer, major trauma, surgery, recent hospitalization, long flights, immobility, obesity and accompanying heart diseases.<sup>2</sup> These risk factors are thought to increase intravascular coagulation, leading to venous thromboembolism. Factors causing intravascular clotting; it was defined by Virchow in 1856 as "1. vascular endothelial damage 2. hypercoagulability 3. stasis". In 75% of VE cases, acquired and/or hereditary factors causing one of these three factors are detected.<sup>3</sup> In PE, a series of pathophysiological events are triggered by the settling of the thrombus in the lungs. The number and diameter of the occluded vessels, the size of the embolism, the patient's cardiopulmonary reserve, reflex vasoconstriction due to pulmonary artery dilation, inflammatory mediators, vasoconstriction due to serotonin, thromboxane and fibrinogen degradation product fibropeptide B secreted from platelets affect the pathophysiological events and clinical findings in PE.<sup>4,5</sup>

Correct treatment of the disease is as important as diagnosing it. Pulmonary thromboembolism has a high clinical suspicion and moderate clinical probability, and anticoagulant therapy should be initiated in patients with a low risk of bleeding while awaiting test results.

Once the diagnosis is confirmed, LMWH or standard heparin (SH) should be started. This treatment should be continued for at least five days. Oral anticoagulant is added to the treatment within the first 24 hours. In those with low bleeding risk, giving 10 mg warfarin in the first two days allows the INR value to reach  $\geq 2$  more quickly, thus shortening the hospital stay. It is recommended to start warfarin treatment at a dose of 5 mg/day in patients with bleeding risk and in elderly patients (>75 years of age). When the INR value is found to be between 2.0-3.0 for two consecutive days, heparin is discontinued and treatment is continued with oral anticoagulant only for at least three months. Initial treatment is three weeks for rivaroxaban and seven days for apixaban. If the patient's initial treatment was with an oral direct factor Xa inhibitor (rivaroxaban or apixaban), maintenance treatment is continued with the maintenance dose of the same drug. Oral direct thrombin inhibitor (dabigatran) or direct factor Xa inhibitor (edoxaban) can also be used instead of warfarin in maintenance treatment.<sup>6</sup>



Reperfusion therapy can be lifesaving in cases with high mortality risk. Systemic thrombolytic therapy is the most commonly used treatment for reperfusion purposes. In recent years, interventional treatments with percutaneous catheters have begun to be used with increasing frequency. In cases where neither can be used or are not effective, the only option is surgical embolectomy. In cases of pulmonary thromboembolism, thrombolytic drugs, which actively dissolve the thrombus, provide rapid improvement in pulmonary perfusion, hemodynamics, and gas exchange and right ventricular functions. This improvement is most evident when given within the first 48 hours of the onset of symptoms, but has also been shown to be beneficial when given within 14 days. Clinical improvement with thrombolytic therapy in patients with high mortality risk and right ventricular recovery demonstrated by transthoracic echocardiography (TTE) after 36 hours have been demonstrated in 98% of patients given thrombolysis.<sup>7,8</sup> In patients with moderate-high risk PTE who cannot receive thrombolytic treatment due to the risk of bleeding, who cannot respond to thrombolytic treatment, or whose critical condition does not allow waiting for the effective time of systemic thrombolytic treatment, or who have a tendency to hemodynamic deterioration, selected massive (high risk) PE can be treated with a percutaneous catheter if sufficient experience is available. Reperfusion therapy can be tried by performing interventional treatment.<sup>9</sup> The aim of catheter-based interventions is to quickly reduce pulmonary artery pressure, right ventricular load and pulmonary vascular resistance, increase systemic perfusion and improve right ventricular functions. Intrapulmonary thrombolytic therapy has no advantage over systemic administration. With thrombolytic therapy, the obstruction in pulmonary blood flow in the early stages of acute PE is rapidly eliminated, lung blood supply is restored, sPAP decreases, and thus cardiogenic shock is prevented. Agents such as streptokinase, urokinase, alteplase and tissue plasminogen activator (tPA) are used as thrombolytic agents. However, in catheter-guided thrombolytic treatments, tPA is used more frequently due to the low incidence of side effects and rapid onset of action.<sup>10</sup>

## CONCLUSION

In case of recurrent thromboembolism, especially in massive PE cases that develop due to chronic DVT, as in our patient, percutaneous intravascular thrombolytic therapy should be considered as an alternative to systemic thrombolytic therapy and patients should also be evaluated in terms of thrombolytic treatment with EKOS.

## ETHICAL DECLARATIONS

### Informed Consent

The patient signed and free and informed consent form.

### Referee Evaluation Process

Externally peer-reviewed.

### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

### Financial Disclosure

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## Author Contributions

All the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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# Inguinal hernia coexisting with spermatic cord leiomyoma

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Dear Editor,

Leiomyomas are most commonly found in the uterus, followed by the small bowel and esophagus. Although rare, there have been limited reports of leiomyomas arising from the genitourinary system, which includes the bladder, epididymis, prostate, testis, and penis.<sup>1,2</sup> Scrotal leiomyomas, classified within the category of genital leiomyomas, present as solitary growths of uncertain origin and can manifest within various scrotal structures, such as the epididymis, spermatic cord, tunica albuginea, or scrotal wall. They exhibit a gradual growth pattern over time. It is noteworthy that spermatic cord leiomyoma represents an exceptionally rare condition, with fewer than thirty cases documented in the medical literature since the 1950s.<sup>3</sup>

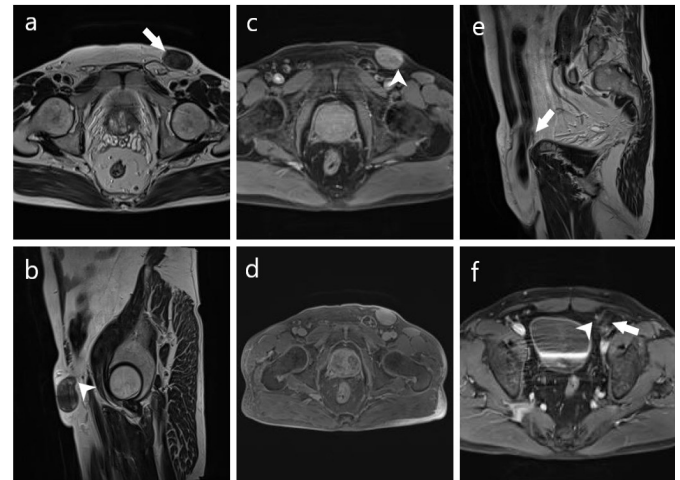
This study aims to delineate the clinical and radiological attributes of the infrequently encountered spermatic cord leiomyoma and discern its differential diagnosis.

A 63-year-old male patient presented to the general surgery clinic with complaints of pain and swelling in the left groin. Upon taking the medical history, it was revealed that the patient had been experiencing swelling for an extended period, intermittently accompanied by pain. The patient had no known pre-existing medical conditions or prior surgical history. Physical examination revealed the presence of a reducible hernia in the left inguinal region, along with the palpation of a mobile, solid mass measuring approximately 3 cm in diameter.

An ultrasound (US) examination was performed on the patient, which revealed a well-defined solid hypoechoic lesion measuring approximately 35x25 mm. This lesion exhibited minimal vascularity, without any evidence of hilar vascularity. Both testicles were visualized within the scrotal sac. In the differential diagnosis, conditions such as lymphadenopathy, desmoid tumor, and paratesticular tumors, such as spermatic cord tumors, were considered due to the inguinal location of the mass. To further characterize the lesion, magnetic resonance imaging (MRI) was conducted.

The MRI imaging identified a solid lesion in the left inguinal region measuring 37x24 mm, displaying an ovoid appearance (Figure 1). This lesion was iso-hypointense relative to

the adjacent muscle tissue on T2-weighted imaging and exhibited hyperintensity on fat-saturated T1-weighted images compared to muscle tissue. Additionally, a hyperintense rim was observed on fat-saturated T1-weighted images. Post-contrast T1-weighted images demonstrated moderate contrast enhancement. Sagittal images revealed a tail-like appearance, suggesting its origin from the spermatic cord. Notably, tumor markers and blood values were entirely within normal ranges.

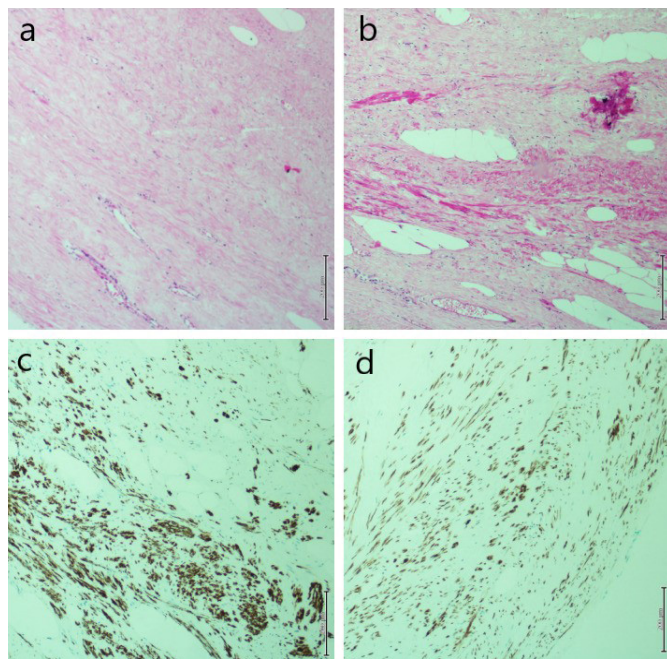


**Figure 1.** Indirect Inguinal Hernia with Spermatic Cord Leiomyoma  
In the T2-weighted (T2W) axial (a) and sagittal (b) Magnetic Resonance Imaging (MRI) images, a hypointense lesion (arrow) with a tail-like appearance (arrowhead), presumed to originate from the spermatic cord, is observed. Additionally, the fat-saturated T1-weighted (T1W) image (c) shows hyperintensity compared to muscle tissue, with the presence of a hyperintense rim (arrowhead). Moderate contrast enhancement is demonstrated in the T1W subtraction image (d). The T2W sagittal (e) and T1W axial (f) MRI images illustrate the indirect inguinal hernia, with the hernia defect (arrow) located laterally to the inferior epigastric artery (arrowhead).

The patient underwent a surgical procedure comprising hernia repair and mass excision. A standard inguinal incision was made to access the surgical site, followed by meticulous dissection of the spermatic cord to expose the mass, the etiology of which remained unknown. Care was taken to preserve vital adjacent structures such as the vas deferens and testicular vessels. The mass was excised precisely, ensuring complete removal while minimizing disruption to neighboring anatomical elements. Concurrently, hernia repair was performed using a standardized technique,

addressing the inguinal hernia and ensuring inguinal canal closure to prevent recurrence. Following the surgical procedure, the patient experienced an uneventful recovery and was discharged from the hospital after a two-day stay.

In the excised mass, the Hematoxylin-Eosin (H&E) staining revealed focal lipocytes and areas of hyaline degeneration amidst smooth muscle fibers. Additionally, cytoplasmic staining was observed in smooth muscle cells and fibers through Desmin and Muscle Specific Actin (MSA) staining (Figure 2). Based on these findings, a diagnosis of leiomyoma was established.



**Figure 2.** Leiomyoma Microscopy (a) and (b) Hematoxylin-Eosin (H&E) staining, showing focal lipocytes and areas of hyaline degeneration between smooth muscle fascicles. (c) Desmin staining, indicating cytoplasmic staining in smooth muscle cells. (d) Muscle Specific Actin (MSA) staining, demonstrating cytoplasmic staining in smooth muscle fibers. Magnification: 10x.

Written informed consent was obtained from the patient.

Spermatic cord tumors constitute a rare and heterogeneous group of neoplasms. They are predominantly benign in origin, with malignant tumors being exceedingly rare. Benign tumors within this category include lipoma, leiomyoma, rhabdomyoma, cellular angiofibroma, hemangioma, and aggressive angiofibroma.<sup>4</sup> In our case, as in many instances, spermatic leiomyomas present as slow-growing solitary masses in the paratesticular or inguinal region and can mimic hernias. In our case, a solitary mass was accompanied by a hernia.<sup>3</sup>

The MRI findings played a pivotal role in the diagnostic process. The lesion's hypointensity on T2-weighted MRI images allowed us to exclude lipoma, cellular angiofibroma, aggressive angiofibroma, and hemangioma as potential diagnoses. Furthermore, the characteristic tail-like appearance on sagittal imaging led us to rule out lymphadenopathy, given the lesion's presumed origin from the spermatic cord. Additionally, desmoid tumors were not considered due to the absence of a surgical history and lack of association with the abdominal wall. Consequently, the MRI characteristics strongly supported the diagnosis of leiomyoma.

Inguinal Region Solitary Masses have a considerably broad range of differential diagnoses, and MRI plays a valuable role in their diagnosis. As in our case, scrotal leiomyoma typically manifests in the fifth decade of life and exhibits slow growth. Literature has also reported cases with bilateral involvement.<sup>5</sup> They can be associated with hydrocele and hernia. Malignancy cannot be ruled out, and surgical excision is often necessary in such cases.

In summary, this case report highlights the rare occurrence of spermatic cord leiomyoma and emphasizes the role of MRI in its accurate diagnosis. Although benign, this slow-growing tumor can mimic hernias, necessitating surgical excision for definitive diagnosis and management. This case underscores the importance of considering leiomyoma in the differential diagnosis of inguinal masses and the valuable role of MRI in preoperative assessment.

**Keywords:** Inguinal hernia, spermatic cord, leiomyoma, magnetic resonance imaging (MRI), surgical excision

## ETHICAL DECLARATIONS

### Informed Consent

The patient signed and free and informed consent form.

### Referee Evaluation Process

Externally peer-reviewed.

### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

### Financial Disclosure

The authors declared that this study has received no financial support.

### Author Contributions

All the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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