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Comparative examination of patients with suspect and diagnosis of prostate cancer before and during the COVID-19 pandemic

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ABSTRACT

Aims: We aimed to determine the clinical stage (CS) alteration in recently diagnosed prostate cancer (PCa) patients with a delay in outpatient diagnostic evalutions and procedures due to COVID-19.

Methods: We reviewed patients that underwent 12 quadrant biopsies in our clinic between January 2018 and April 2022, 86 pre-pandemic (group-1) and 86 pandemic admission. The outcomes of patients with PCa, during pandemic (group-2) were evaluated cross-sectionally. Serum PSA levels, prostate volume, biopsy parameters, Gleason score and groups, CS, presence of high and low volume metastatic disease, clinical risk assessments were compared in both groups.

Results: In group-1, 440 patients were included and PCa was reported in the pathology results of 86 patients (19.54% of biopsies performed). Group-2 encompassed 287 patients in which we identified 86 patients with PCa. We identified PCa in 29.96% of biopsies performed in the group-2. Probablity of encountering a malignant prostate biopsy was found to be significantly higher in the group-1 (p=0.001). The median CS was T2b in group-1, and T2c in group-2 which was found statistically significant (p=0.019). The number of cancer-positive cores was 4 in group-1 and 5 in group-2 (p=0.007). The average values of tumor percentages in cancerous cores were determined as 47% in group-1 and 57% in group-2 (p=0.024). The probability of a patient with a malignant biopsy being in the local stage is higher in group-1 (p=0.043).

Conclusion: Serum PSA levels, CS, number of cancer-positive cores and average tumor percentages in cancerous cores during the pandemic are significantly higher compared to the group-1. Postponing prostate biopsy in suspected PCa; may negatively affect disease-related survival or overall survival.

Keywords: COVID-19, pandemic, prostate cancer

INTRODUCTION

Timespan during the diagnosis and treatment of PCa, does not affect outcome in patients with low-risk disease. However, treatment delay may have a detrimental effect in high-risk patients.[1] The observed decline in these common screening and diagnostic procedures reflects the impact of the COVID-19 pandemic on early detection and points to possible downstream effects on the timing and staging of future cancer diagnoses.[2] The reduction of the number of patients undergoing prostate biopsies and outpatient screening, which were inevetiably postponed during the COVID-19 period, may have caused patients to be subject to higher risk classes and Gleason scores in the future.

A comprehensive review of the literature, relays studies on PSA screening and cases of delayed prostate biopsy with multiparemetric MRI and high PI-RADS score during the COVID-19 pandemic. Accordingly, it has been shown that when men with PI-RADS 5 lesions and no previous biopsy screened earlier, a delay of up to 8 months between imaging and biopsy does not affect subsequent findings.[3]

The aim of this study is to investigate the effect of delay due to COVID-19 pandemic on prostate biopsy outcomes and clinical stages (CS) of the patients who were unable to have an appointment to an outpatient clinic and have routine prostate examination along with screening tests timely.

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METHODS

Ethics

The study was conducted with the permission of the Non-interventional Researches Ethics Committee of Kırıkkale University (Date: 10.02.2022, Decision No: 2022.02.03). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The clinical records of 172 male patients between the ages of 49 and 87, who were diagnosed with prostate cancer (PCa) between January 2018 and April 2022, were retrospectively collected from electronic archive of Kırıkkale University Hospital for the study. The decision to perform a prostate biopsy was made based on serum PSA elevation, suspicion of malignancy on digital rectal examination (DRE), and/or suspicious image parameters on magnetic resonance imaging.

Patient Selection Criteria

- Having received PCa diagnosis in between Jan 2018 and Apr 2022.
- Being able to give informed consent for the study and having an adequate mental state to give written consent
- Not having secondary malignancy or any disesase affecting 10 year survival outcome of the patient. (e.g. Terminal stage malignancy, refractory HIV infection, terminal bone marrow diseases…)
- Adherence to follow-up appointments
- Having a minimum of blood work-up of PSA, BUN, cretainine and radiological study of bone scintigrphy, contrast enhanced thoracal and abdominal CT.

Patients; Age, serum total PSA value, DRE findings, prostate volume, clinical PCa stages, metastasis volumes, Gleason score, Gleason grade group, number of positive cores, and average tumor percentage in positive cores were examined and recorded.

Serum PSA values of the patients; It was run on a Roche-Cobas E801 device with the Roche-PSA 801 kit. DRE was performed by two different urologists. All patients underwent prostate biopsy under TRUS guidance and intrarectal local anesthesia containing lidocaine-prilocaine combination. TRUS; It was performed using the Voluson P8 ultrasonography device and standard rectal probe. Before the procedure, patients were given standard ciprofloxacin prophylaxis and an enema was administered.

Patients; Considering that COVID-19 was declared a pandemic by the World Health Organization (WHO) on March 11, 2020, it was divided into two: before and after this date. Group-1; Patients who underwent prostate biopsy between 01.2018 and 01.2020 were recorded as the pre-pandemic group. Group-2; During the pandemic period, patients who underwent prostate biopsy between 03.2021-04.2022 were determined as a group. During the approximately 14-month period, no prostate biopsy was performed in our clinic due to the postponement of elective procedures and disruption of outpatient services.

Statistical Analysis

The obtained data were statistically analyzed with the Statistical Package for Social Sciences (SPSS) 20.0 program. Normality evaluation of the parameters was done with the Shapiro-Wilk test. Non-parametric evaluations between independent groups were made with the Mann Whitney-U test, results are presented as median and interquartile range. Normally distributed parameters were evaluated with t test. Numerical variables are summarized by mean, standard deviation, min, max. p values less than 0.05 were considered statistically significant. Categorical variables were evaluated with the Chi-square test.

RESULTS

Prostate biopsy was performed on 440 patients in the pre-pandemic group, and the pathology result of 86 patients was reported as prostate adenocarcinoma. 19.54% of the biopsies performed before the pandemic were diagnosed with prostate adenocarcinoma. During the pandemic period, 287 patients underwent prostate biopsy to reach a diagnosis of prostate adenocarcinoma, 86 of whom were in the group. 29.96% of the biopsies were reported as prostate adenocarcinoma. The rate of encountering malignant prostate biopsy results was found to be statistically significantly higher in the pandemic group ($p<0.01$). Clinicopatolocigal features of patiens were given in Table 1 hollistically.

Table 1. Descriptive characteristics of patients

Parameters	n (%)
Patient group	
Before pandemic	86 (50.0)
During the pandemic	86 (50.0)
Findings of digital rectal examination	
Normal	64 (37.2)
Abnormal	108 (62.8)
T stage	
T1c	339 (19.2)
T2a	24 (14.0)
T2b	35 (20.3)
T2c	33 (19.2)
T3a	21 (12.2)
T3b	24 (14.0)
T4a	2 (1.2)
Gleason score	
6	57 (33.1)
7	40 (23.3)
8	44 (25.6)
9	29 (16.9)
10	2 (1.2)
Gleason grade group	
1	57 (33.1)
2	21 (12.2)
3	18 (10.5)
4	46 (26.7)
5	30 (17.4)
	Mean±SD
Age	66.85±7.28
Serum total PSA	20.53±22.59
Prostate volume	47.90±10.95
Number of cancer positive cores	4.68±3.11
Tumor pertencage of cancer positive cores	51.60±28.49

SD: Standard deviation

Table 2 thoughroughly covers the numerical patient characteristics; whereas Table 3 covers categorical variables in both groups. The median values of serum PSA levels of "before-pandemic" and "during-pandemic" groups were determined as 11.00-12.55, respectively. Serum PSA levels

were statistically significantly higher during the pandemic period (p=0.046). The mean prostate volume between the groups were determined as 48.14+11.03 (min:26, max:96) and 48.00+9.88 (min:28, max:69) (p=0.930).

Table 2. Distribution of data before and during the pandemic according to some characteristics

Parameters	Before pandemic Mean±SD (min-max)	During the pandemic Mean±SD (min-max)	Test
Age	67.35±7.57 (49-87)	66.35±6.98 (49-87)	t=0.900 p=0.369
Prostate volume	48.14±11.03 (26-96)	48.00±9.88 (28-69)	t=0.087 p=0.930
	Median	**Median**	
Serum total PSA (IQR)	11.00 (13.4-20.6)	12.55 (18.27-29.8)	MWU=3045.500 p=0.046
Number of cancer positive cores, (IQR)	3.00 (3.49-4.74)	4.50 (4.55-5.93)	MWU=2830.500 p=0.007
Tumor pertencage of cancer positive cores (IQR)	50.00 (40.34-50.91)	60.00 (50.80-62.34)	MWU=2963.500 p=0.024

SD: Standard deviation, Min: Minimum, Max: Maximum, IQR: Interquartile range

Table 3. Chi-square test results for nonparametric variables

Clinicopathological parameters		Before pandemic n (%)	During the pandemic n (%)	p value
T stage	T1c	24 (27.9)	9 (10.5)	p=0.015
	T2a	13 (15.1)	11 (12.8)	
	T2b	15 (17.4)	20 (23.3)	
	T2c	15 (17.4)	18 (20.9)	
	T3a	5 (5.8)	16 (18.6)	
	T3b	12 (14)	12 (14)	
	T4a	2 (2.3)	0	
Gleason score	6	35 (40.7)	22 (25.6)	p=0.029
	7	13 (15.1)	27 (31.4)	
	8	24 (27.9)	20 (23.3)	
	9	14 (16.3)	15 (17.4)	
	10	0	2 (2.3)	
Gleason grade group	1	35 (40.7)	22 (25.6)	p=0.036
	2	8 (9.3)	13 (15.1)	
	3	4 (4.7)	14 (16.3)	
	4	25 (29.1)	21 (24.4)	
	5	14 (16.3)	16 (18.6)	

Data are expressed as frequencies with percentages in parentheses (n (%))

Intergroup diffences of DRE of the patients yielded to be statistically insignificant(p>0.05). While the T2b stage had the highest frequency in group-1, T2c stage occured to have the highest frequency in group-2 (p=0.015).

Gleason score and Gleason grade group were both significantly higher in group-2 (p<0.05).

The median of tumor percentages in cancer-positive cores were determined as 50 in group-1 and 60 in group-2. The difference between the tumor percentages in cancer-positive cores between the two groups was found to be statistically significant (p=0.024).

While 47.67% (41 patients) of prostate adenocarcinoma patients in the group before the pandemic were in the clinical local stage, 32.55% (28 patients) of the prostate adenocarcinomas in the group during the pandemic were detected in the clinical local stage. The probability of the patient undergoing malignant biopsy being in the clinical local stage was found to be statistically significantly higher in the pre-pandemic group (p=0.043).

Before the pandemic, 17.44% (15 patients) of the group were detected in the clinically locally advanced stage and 34.88% (30 patients) in the metastatic stage. These rates were 19.76% (17 patients) and 47.67% (41 patients), respectively, in the group during the pandemic. The probability of a patient with malignant biopsy being in the clinically locally advanced or metastatic stage is similar in both groups (p>0.05).

When metastatic patients in both groups were divided into low and high volume using Latitude criteria; In the pre-pandemic group, 56.66% (17 patients) of metastatic patients were low volume and 43.33% (13 patients) were high volume. In the group during the pandemic, 46.34% (19 patients) of metastatic patients had low volume metastatic disease and 53.65% (22 patients) had high volume metastatic disease. No statistically significant difference was detected in terms of metastatic disease volume (p>0.05). However, in the pre-pandemic group; The probability of patients in the metastatic stage to have low volume is approximately 1.5 times higher than the group during the pandemic (odds ratio=1.514).

Prostate biopsy was recommended and planned for 25 patients because prostate adenocarcinoma was suspected before the pandemic, but prostate biopsy was performed on these patients with a delay during the pandemic period. 9 of 25 prostate biopsies were reported as prostate adenocarcinoma. In other words, the malignancy detection rate in postponed prostate biopsies was 36%, and it was found to be statistically significantly higher than the group that underwent prostate biopsy before the pandemic (p=0.047). The probability of encountering malignancy was statistically similar between patients whose prostate biopsy was planned and delayed and other patients who underwent prostate biopsy during the pandemic (p>0.05).

Although biopsy was planned, it was performed late during the pandemic period and 9 patients were diagnosed with prostate adenocarcinoma; 3 (33.33%) were detected in the clinical local stage, 2 (22.22%) in the locally advanced stage and 4 (44.44%) in the metastatic stage. All 4 patients in the metastatic stage were in the high-volume metastatic stage. Possibility of encountering local, locally advanced and metastatic stage disease; It was statistically similar for patients who had a planned but delayed biopsy before and during the pandemic (p>0.05). However, the probability of having a malignant biopsy and encountering high-volume metastatic disease was found to be statistically significantly higher in the group where the biopsy was planned before the pandemic and performed with a delay, compared to the pre-pandemic group (p=0.029), (**Figure**).

Radical prostatectomy and extended lymph node dissection operations were performed on patients in the clinical local stage in both groups before and during the pandemic. In the pre-pandemic group, 3 (7.17%) of the 41 patients evaluated at the clinical local stage were evaluated at the pathological locally advanced stage. Of the 28 patients evaluated in clinical local stage during the pandemic, 5 (17.85%) were reported as pathological locally advanced stage and no

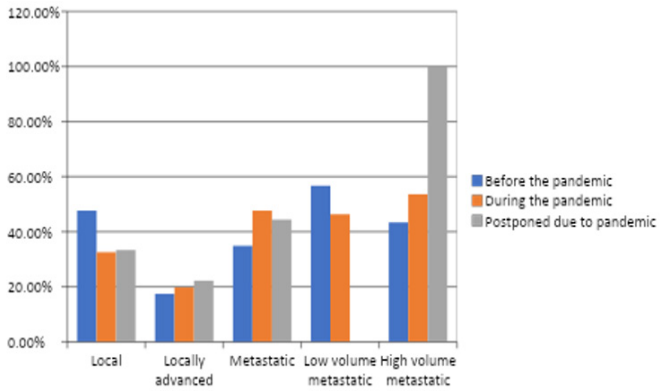

Figure. Stage differences between groups before treatment

statistically significant difference was found between the two groups (p>0.05). However, the need for additional treatment for a patient in the clinical local stage during the pandemic group is approximately 2.5 times higher due to being in a pathologically locally advanced stage (odds ratio=2.489).

According to this study, patients diagnosed with PCa during the pandemic; Serum PSA levels, clinical T stage, gleason score, gleason grade group, number of tumor-positive cores, and percentages of tumors in tumor-positive cores were found to be significantly higher than the pre-pandemic period.

DISCUSSION

The COVID-19 pandemic has presented a unique challenge for cancer patients for several reasons. Patients with cancer may be more likely to contract COVID-19 and have serious adverse outcomes, including intensive care admissions, ventilator requirements, and death.[4-7] For this reason, there is a group who cannot have a prostate biopsy and do not know the diagnosis of cancer and may be at greater risk.

Due to substantial delay caused by the lack of addmission during pandemic patients were subject to increased risk of biochemical recurrence which directly effected the patient's morbidity, mortality and quality of life.[8] Furthermore, theese delays may have caused patients to lose the chance of definitive treatment.[9] The incidence of bone metastasis may have been increased in patients with metastatic disease and delayed diagnosis.[10]

According to the results of our study, the probability of encountering a malignant biopsy result in the group during the pandemic period was found to be higher than in the group in which prostate biopsy was performed before the pandemic. This delay may also be due to an increase in the proportion of symptomatic patients with PCa. That is, compared with opportunistic screening, patients diagnosed with PCa post-pandemic are more likely to be symptomatic than the pre-pandemic group.

The time required to obtain 86 malignant biopsy results was shorter in the pandemic group. This may be attributed to the fact that patients who postponed their examinations and wanted to apply to our polyclinic without further delay as normalization returns.

In a study, 267 patients with localized PCa who were not receiving treatment were followed for approximately 8.5 years and it was found that the prognosis of patients with high initial serum PSA values and PSA rate was worse.[11]

In our study, serum PSA median values of the patients who underwent prostate biopsy during the pandemic period were found to have significantly higher levels of PSA compared to the pre-pandemic group (p<0.05). This may predict that the prognosis of PCa patients detected during the pandemic period may be worse.

In a study published in 2004; 16.321 patients diagnosed with PCa between 1989-1990 and 2001-2002 were compared. It was found that the incidence of T1 tumors increased from 16.7% to 48.5%, and the incidence of T3-4 tumors decreased from 11.8% to 3.5%, respectively.[12] This may be attributable to changes in practice patterns regarding screening and pathological grading.

In this study, the distrubution of the clinical T stages of patients are found to be statistically significantly higher in patients evaluated during the pandemic compared to the group evaluated before the pandemic (p<0.05). This situation may be related to the possible delay in the evaluation and diagnosis of patients due to the COVID-19 pandemic. This difference between patients may eliminate the chance of definitive treatment for patients or may lead to the need forcomplementary treatments in addition to definitive treatment. It may also increase the likelihood of PCa recurrence and positive surgical margins.

According to the D'Amico Risk classification, used to predict the recurrence of non-metastatic PCa; no statistically significant difference was detected between the risk groups of the patients. This may indicate that especially locally and locally advanced stage patients have similar recurrence risks between the groups before and during the pandemic and are not affected by the delay due to the negativities of the pandemic.

Statistically significant difference was detected between the two groups in terms of Gleason score and Gleason ratings of patients diagnosed with PCa before and during the pandemic(p<005). In accordance with this finding studies, high volume cross-sectional studies found that some cancers detected as low and medium risk in prostate needle biopsy actually have higher Gleason scores.[13]

In our study, the number of cancer-positive cores and the percentage of tumors in cancer-positive cores, which may have a high prediction of this risk increase, were found to be statistically significant in patients who underwent prostate biopsy during the pandemic compared to the group before the pandemic (p<0.05). Therefore, due to the pandemic-related measures, the healthcare was stalled and halted throughout the state which utterly caused the postponement of prostate biopsies. In fact, it may have caused the disease to have a higher probability of recurrence and poor prognosis.

Of the 41 patients evaluated in the clinical local stage in the pre-pandemic group, 3 (7.17%) were detected in the locally advanced stage. Of the 28 patients evaluated in the clinical local stage during the pandemic, 5 (17.85%) were reported to have locally advanced stage. A patient in the clinical local stage in the pandemic group is actually in a pathologically locally advanced stage, so the need for additional treatment is approximately 2.5 times higher.

Patients with locally advanced PCa have significantly higher disease-specific mortality rates compared to local stage disease. In five and ten year follow-ups, respectively; Clinical

progression was reported as 22% and 75%, local progression as 22% and 84%, and distant metastasis development as 27% and 56%.[14] In our study, while 47.67% (41 patients) of prostate adenocarcinoma patients in the pre-pandemic group were in the clinical local stage, 32.55% (28 patients) of the prostate adenocarcinomas in the group during the pandemic were detected in the clinical local stage. The probability of the patient with malignant biopsy being in the clinical local stage was found to be statistically significantly higher in the pre-pandemic group. Therefore, it can be expected that the disease-specific mortality, clinical and local progression probabilities of patients diagnosed with PCa in the pre-pandemic group would be lower compared to the period during the pandemic.

The likelihood of a patient with a malignant biopsy being in the clinically locally advanced or metastatic stage is similar in both groups. However, the pandemic-group patients in the metastatic stage are approximately 1.5 times more likely to have high volume than the pre-pandemic group. The prognosis of those with high volume metastatic disease is worse than those with low volume and its treatment is more refractory and costly.[15,16] Some patients with low-volume metastatic PCa may have remained untreated due to the delay and the pandemic and may have been detected as high-volume.

Prostate biopsy was recommended and planned for 25 patients because prostate adenocarcinoma was suspected before the pandemic, but prostate biopsy was performed on these patients with a delay during the pandemic period. 9 of 25 prostate biopsies were reported as prostate adenocarcinoma. Hence, the malignancy detection rate in postponed prostate biopsies was 36% and was found to be statistically significantly higher than the group that had a prostate biopsy before the pandemic. The decision to postpone prostate biopsies during the pandemic period caused us to encounter higher malignancy rates.

There had been considerable lag in the biopsy schedule during the pandemic period and 9 patients were diagnosed with prostate adenocarcinoma; 3 (33.33%) were detected in the clinical local stage, 2 (22.22%) in the locally advanced stage and 4 (44.44%) in the metastatic stage. All 4 patients in the metastatic stage were in the high-volume metastatic stage. Possibility of encountering local, locally advanced and metastatic stage disease was statistically similar for patients who had a delayed biopsy before and during the pandemic. However, the probability of having a malignant biopsy and encountering high-volume metastatic disease was found to be statistically significantly higher in the group in which the biopsy was planned before the pandemic and performed with a delay, compared to the pre-pandemic group.

Limitations

Our study had some limitations. The biggest limitation was that patient outcomes especially those with delayed diagnosis such as long-term morbidity, mortality, and disease-related survival, were unknown. Due to relatively low budget of the healtcare facility where the study was conducted, patients were not evaluated with state-of-the-art radiological studies as Ga-68 PSMA-PET or multiparametric MRI. It was also a relatively small sample size; Therefore, the design of large-scale clinical studies may be encouraged so that the above results can be confirmed with increased statistical power.

CONCLUSION

According to the findings of this cross-sectional study, serum PSA levels, CS, Gleason score, Gleason grade group, number of cancer-positive cores and tumor percentages in cancerous cores were found to be significantly higher in prostate biopsies performed approximately 14 months late due to pandemic fear and postponements, compared to the pre-pandemic period. The probability of a patient with a malignant biopsy being in the clinical local stage was found to be higher in the pre-pandemic period compared to the pandemic period. The probability of the biopsy results being malignant and the probability of encountering high-volume metastatic PCa in patients with suspected malignancy but whose prostate biopsy was postponed due to the pandemic was found to be significantly higher than the group in which prostate biopsy was performed before the pandemic.

From a historical point of view, infectious diseases that can cause intercontinental disease may occur in the future as well. In such cases, postponing prostate biopsy in patients with suspected PCa may negatively effect physical and mental status, disease-related survival or overall survival.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was conducted with the permission of the Non-interventional Researches Ethics Committee of Kırıkkale University (Date: 10.02.2022, Decision No: 2022.02.03).

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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Relationship between pan-immune-inflammation value, systemic immune inflammation index, and systemic inflammation response index in patients with rheumatoid arthritis

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ABSTRACT

Aims: The aim of this study was to develop easily applicable tools that reflect systemic inflammation in rheumatoid arthritis (RA). In this context, the relationship between RA disease activity and pan-immune-inflammation value (PIV), systemic immune-inflammation index (SII), and systemic inflammation response index (SIRI) was examined.

Methods: Patients and healthy controls who applied to Yozgat Bozok University Physical Medicine and Rehabilitation and Internal Medicine clinics between 01.01.2020 and 04.01.2025 were included in the study. Visual Analog Scale (VAS), Disease Activity Score-28 (DAS28), hemogram, and biochemistry parameters—including ALT, AST, fasting glucose, C-reactive protein (CRP), erythrocyte sedimentation rate, uric acid, creatinine, calcium, magnesium, alkaline phosphatase, parathyroid hormone, lipid profile, albumin, total protein, T4, TSH, rheumatoid factor (RF), and anti-cyclic citrullinated peptide (anti-CCP)—were retrospectively recorded from patient files. PIV, SII, and SIRI were calculated using complete blood count data from both the RA and control groups. Data were analyzed using SPSS, and a significance level of 0.05 was considered statistically significant.

Results: SII, SIRI, and PIV values were significantly higher in the RA group compared to the control group (p=0.002, p=0.001, and p=0.001, respectively). Among the three disease activity groups, SII, SIRI, and PIV levels were highest in the active disease group. A positive correlation was found between DAS28 and SII (r=0.305, p=0.012), and between DAS28 and PIV (r=0.270, p=0.028). However, no significant correlation was observed between DAS28 and SIRI (p=0.111). The difference among the activity groups was statistically significant for SII and PIV (p=0.016 and p=0.039, respectively), but not for SIRI (p=0.171). Furthermore, SII and PIV levels were significantly higher in patients receiving anti-TNF-α treatment compared to those using DMARDs (p=0.001 and p=0.003, respectively).

Conclusion: The significantly higher SII and PIV values in the RA group compared to controls, and their positive correlation with DAS28, suggest that these indices may be associated with RA disease activity. Additionally, the lower levels of SII and PIV in patients receiving anti-TNF-α treatment support their potential role in monitoring treatment response.

Keywords: Rheumatoid arthritis, disease activity, pan-immune-inflammation value, systemic immune-inflammation index, systemic inflammation response index

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, systemic inflammatory disorder that predominantly targets small joints, resulting in both structural damage and functional limitations, and ultimately diminishing quality of life.[1] The precise cause of RA remains unknown; however, the disease is characterized by inflammation that initially affects the synovial membrane and progressively damages the underlying subchondral bone and cartilage. This pathological process promotes the development of pannus tissue, which plays a key role in joint deformities and irreversible damage. Although the exact mechanisms underlying RA pathogenesis are not fully clarified, immune system dysregulation is believed to be central to disease progression. Accurate assessment of disease activity is essential not only to avoid serious complications but also to initiate timely and effective therapeutic interventions.[2] DAS28 is a widely used assessment tool for determining disease activity in RA and monitoring response to treatment.[3]

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RA is an inflammatory condition involving the immune system. Currently, there is no single laboratory test that definitively confirms the diagnosis of RA. While erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are frequently used to assess inflammation in RA, their diagnostic accuracy is limited due to low sensitivity and specificity.[4] As a result, recent research has focused on identifying new immune-based prognostic indicators such as the monocyte-to-lymphocyte ratio (MLR), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) in the context of RA.[5] Although each of these immune cell types contributes to the inflammatory process, none is sufficient on its own to accurately reflect the overall inflammatory status. Therefore, more integrated indices have been developed that combine these parameters. One such index is the pan-immune-inflammation value (PIV), which is calculated using complete blood count (CBC) data including neutrophils, platelets, monocytes, and lymphocytes and is used to assess the degree of systemic inflammation. PIV has been shown to serve as a prognostic marker in several types of cancer.[6]

The systemic immune inflammation index (SII) increases with relatively high neutrophil and platelet counts and low lymphocyte counts, which is considered an indicator of a strong inflammatory response.[7] SII has been evaluated in diseases such as lupus, psoriatic arthritis, and RA, and is associated with disease activity levels.[6,8,9] The systemic inflammation response index (SIRI) represents the interplay between inflammatory activity and immune function.[10] Several studies have emphasized the importance of SIRI as a biomarker in both the onset and progression of various types of cancer.[11,12]

The aim of our study is to develop easily applicable tools that reflect systemic inflammation in RA. Despite the growing interest in systemic inflammation markers, studies that specifically compare the relationship between RA and indices such as PIV, SII, and SIRI remain limited; therefore, the present study aims to investigate the association between rheumatoid arthritis disease activity and the calculated values of SII, SIRI, and PIV.

METHODS

Ethics

The study was carried out with the permission of the Yozgat Bozok University Non-interventional Clinical Researches Ethics Committee (Date: 04.06.2025, Decision No: 2025-GOKAEK-2511_2025.06.04_526). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. This study included patients who presented to the Physical Medicine and Rehabilitation and Internal Medicine clinics of Yozgat Bozok University between January 1, 2020, and January 4, 2025, and was retrospectively analyzed.

Inclusion Criteria

Diagnosis of RA according to the American College of Rheumatology (ACR) 2010 classification criteria.[13]

- Age between 18 and 75 years

Exclusion Criteria

- Age under 18 or over 75 years
- Historyof malignancy (cancer) or presence of active malignany
- Active infection
- Immunodeficiency
- Presence of hematological diseases or other systemic inflammatory diseases
- Use of steroids or cytotoxic drugs

A healthy control group was also included for comparison. In addition, during the same years, individuals who had applied to the mentioned clinics and tested negative for RA were also included in the study as healthy male and female control subjects.

Inclusion Criteria

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Inflammatory Indices

PIV, SII, and SIRI values were calculated from CBC data in patients diagnosed with RA and in the control group.[14]

These markers are formulated as follows:

PIV=Neutrophils (10^9/L)×platelets (10^9/L)×monocytes (10^9/L)/lymphocytes (10^9/L)

SII=Neutrophils (10^9/L)×platelets (10^9/L)/lymphocytes (10^9/L)

SIRI=Neutrophils (10^9/L)×monocytes (10^9/L)/lymphocytes (10^9/L)

Demographic Data and Laboratory Parameters

For the patients diagnosed with RA included in the study, data were retrospectively collected from patient records, including age, gender, disease history, medications used, and available clinical scores such as The Visual Analog Scale (VAS) and DAS28. Laboratory results recorded included CBC and biochemical parameters such as ALT (U/L), AST (U/L), fasting glucose (mg/dl), CRP (mg/L), sedimentation rate, uric acid (mg/dl), creatinine (mg/dl), calcium, magnesium, alkaline phosphatase, parathormone, lipid profile, albumin, total protein, thyroid function tests (T4 and TSH), rheumatoid factor (RF), and anti-citrullinated peptide antibody (Anti-CCP). Only the parameters that were reviewed and documented in the patient files were included in the study.

VAS

VAS is a reliable and valid tool used to measure pain intensity on a single continuum. This scale consists of a 10-centimeter horizontal line with endpoints labeled “no pain” and “the worst imaginable pain.” Patients mark a point on the line

that best represents their current level of pain. The score is determined by measuring the distance in centimeters from the "no pain" end to the patient's mark, yielding a value between 0 and 10.[15]

DAS28

The DAS28 is a clinical scoring system used to assess disease activity in patients with RA. This score evaluates how active the disease is by considering the number of tender and swollen joints out of 28 specified joints, the patient's self-assessment of their health (usually measured on a visual analog scale ranging from 0 to 100), and inflammatory markers such as ESR or CRP. In our study, we used the DAS28 score calculated with ESR. The formula used for DAS28 calculation was:

DAS28=0.56×√(number of tender joints out of 28)+0.28×√number of swollen joints out of 28)+0.70×ln(ESR)+0.014×patient's global health assessment.

Based on DAS28 scores, patients were categorized into three groups:

DAS28≤3.2: Low disease activity or remission

3.2<DAS28≤5.1: Moderate disease activity

DAS28>5.1: High disease activity or active disease.[16]

Statistical Analysis

The data analyses were performed using SPSS version 20.0 (Statistical Package for the Social Sciences, SPSS Inc., Chicago, IL). Descriptive statistics were presented as mean±standard deviation for continuous variables and as percentages for categorical variables. The Kolmogorov-Smirnov test was used to assess the normality of distribution for the groups. For comparisons between groups, independent samples t-test and ANOVA were used for normally distributed continuous variables, while the chi-square test was applied for categorical variables. In cases where the data were not normally distributed, the Mann-Whitney U test and Kruskal-Wallis test were employed. Correlation analyses (Pearson or Spearman) were conducted to evaluate relationships between quantitative variables. A p-value less than 0.05 was considered statistically significant.

RESULTS

The study included 63 patients with RA (42 females [66%], 21 males [34%]) and 50 healthy controls (32 females [64%], 18 males [36%]). There was no statistically significant difference in gender distribution between the groups (p>0.05). The mean age of all participants was calculated as 63.50±2.12 years. No statistically significant difference was observed between the patient and control groups regarding mean age (p=0.15). In the patient group, the mean disease duration was 12.95±8.94 years; the mean RF level was 171.61±50.60; and the mean Anti-CCP level was 339.33±66. In the patient group, SII, SIRI, and PIV values were found to be statistically higher compared to the control group, and the differences were statistically significant (p=0.002, p=0.001, and p=0.001, respectively) (Table 1).

When patients were classified according to their DAS28 scores into remission, moderate activity, and active disease groups, 24 patients (38%) were in remission, 18 patients (29%) had moderate disease activity, and 21 patients (33%) had active disease. Approximately 69% of the patients were using DMARDs (disease-modifying anti-rheumatic drugs), while 31% were receiving anti-TNF-α therapy. Among those on DMARDs, 80% were using methotrexate, 10% were on other DMARDs besides methotrexate, and 10% were on combination DMARD therapy with methotrexate and another DMARD. Among the patients receiving Anti-TNF-α treatment, 9 were using etanercept, 5 infliximab, 3 golimumab, and 2 adalimumab. Figure 1 displays distribution of disease activity according to DAS Scores. Figure 2 displays distribution of medications used.

Table 1. Mean SII, SIRI, and PIV values of patient and control groups

		Mean	SD	p
SII	Patient	971.11	913.848	**0.002**
	Control	567.22	476.282	
SIRI	Patient	1.594	1.3895	**0.001**
	Control	1.000	.8814	
PIV	Patient	497.15	484.944	**0.001**
	Control	239.36	178.742	

SD: Standard deviation, SII: Systemic immune-inflammation index, SIRI: Systemic inflammation response index, PIV: Pan-immune-inflammation value

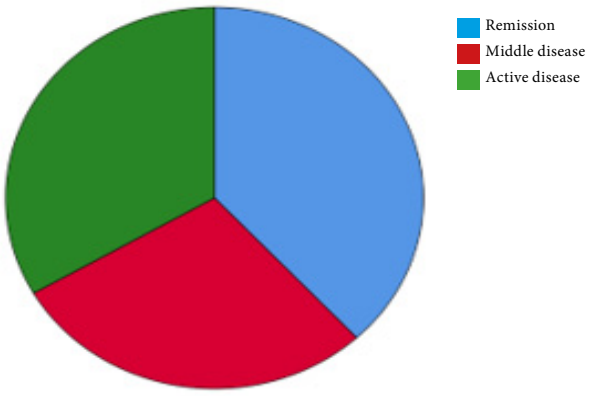

Figure 1. Distribution of disease activity according to DAS scores
DAS: Disease Activity Score

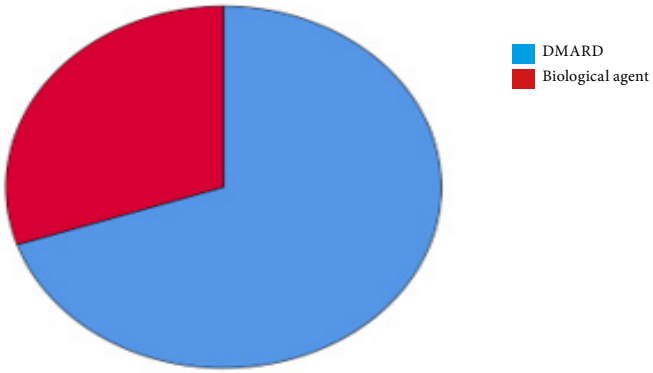

Figure 2. Distribution of medications used

When evaluating the three groups according to disease activity in terms of inflammatory indices, the active disease group showed the highest levels of SII, SIRI, and PIV. The differences between groups were statistically significant for SII and PIV (p=0.016 and p=0.039, respectively), whereas the difference in SIRI levels was not statistically significant (p=0.171) (Table 2). In pairwise comparisons, there were no statistically significant differences in SII, SIRI, and PIV values between the remission and moderate disease activity

groups (p=0.170, 0.819, and 0.322, respectively). Comparing remission and active disease groups, significant differences were observed in SII and PIV values (p=0.013 and p=0.022, respectively), but no significant difference was found for SIRI (p=0.099). Between the moderate and active disease groups, SII levels differed significantly (p = 0.032), while no statistically significant differences were found for SIRI and PIV (p=0.119 and p=0.065, respectively) (Table 2).

Table 2. SII, SIRI, and PIV values according to disease activity

Disease activity	SII (mean±SD)	SIRI (mean±SD)	PIV (mean±SD)
Remission	799.44±909.98	1.35±1.13	404.24±484.44
Moderate	747.93±387.35	1.33±0.90	389.97±221.21
Active	1358.60±1127.	2.10±1.85	695.20±596.38

SD: Standard deviation, SII: Systemic immune-inflammation index, SIRI: Systemic inflammation response index, PIV: Pan-immune-inflammation value

Patients receiving anti-TNF-α therapy had significantly higher SII and PIV levels compared to those using DMARDs (p=0.001 and p=0.003, respectively). However, no significant difference was observed between the two groups in terms of SIRI levels (p=0.116) (Table 3).

Table 3. SII, SIRI, and PIV values according to current treatments in RA patients

Treatment	Index	Mean	SD
DMARD	SII	1148.44	1028.46
	SIRI	1.75	1.51
	PIV	585.59	585.15
Anti-TNF-α	SII	580.47	307.99
	SIRI	1.23	1.01
	PIV	293.37	203.4

DMARD: Disease-modifying anti-rheumatic drugs, SD: Standard deviation, SII: Systemic immune-inflammation index, SIRI: Systemic inflammation response index, PIV: Pan-immune-inflammation value, RA: Rheumatoid arthritis

A moderate positive correlation was found between DAS28 and SII, and a weak positive correlation between DAS28 and PIV (r=0.305, p=0.012; r=0.270, p=0.028, respectively). However, no significant correlation was observed between DAS28 and SIRI (p=0.111). CRP levels showed a moderate positive correlation with SII (r=0.321, p<0.001). RF demonstrated a weak positive correlation with both SII and SIRI, and a moderate positive correlation with PIV (r=0.250, p=0.043; r=0.291, p=0.017; r=0.333, p=0.006, respectively). Additionally, RF levels showed a moderate positive correlation with DAS28 (r=0.341, p=0.005) (Table 4).

DISCUSSION

In this study, we analyzed and compared several inexpensive, simple, and easily accessible inflammation markers derived from CBC, focusing on PIV, SII, and SIRI. While markers like NLR and PLR have been extensively studied in RA, data on PIV, SII, and SIRI remain limited. Our findings showed that systemic inflammation indices SII, PIV, and SIRI were significantly elevated in RA patients compared to controls, with the highest levels observed in the active disease group. Importantly, positive correlations between SII and PIV values and the DAS28 disease activity score suggest their potential utility in assessing disease activity. Given the increasing need for simple, cost-effective, and reliable markers to monitor RA and predict complications early, these inflammation indices hold considerable promise for disease management. In our comparisons between remission and active disease groups, SII and PIV demonstrated potential predictive value, while only SII significantly differentiated between moderate and active disease activity.

The predictive value of SII and PIV regarding disease activity has been explored in previous studies.[14,17] In the study conducted by Yoshikawa et al.[18] involving 574 RA patients, a significant positive correlation was found between SII and

Table 4. Correlation of SII, SIRI, and PIV with other parameters

	DAS28	VAS	ESR	CRP	RF	CCP	SII	SIRI	PIV
DAS28	1	.555**	.420**	.431**	.341**	-.018	.305*	.203	.270*
		.000	.001	.000	.183	.891	.015	.111	.032
VAS		1	.096	.132	-.024	.022	.151	.028	.098
			.455	.302	.851	.864	.237	.828	.444
ESR			1	.516**	.336**	.303*	.432**	.250**	.388**
				.000	.007	.016	.000	.008	.000
CRP				1	.069	.006	.321**	.173	.258**
					.589	.962	.001	.067	.006
RF					1	.547**	.250*	.291*	.333**
						.000	.048	.021	.008
CCP						1	.030	.102	.050
							.818	.425	.700
SII							1	.693**	.877**
								.000	.000
SIRI								1	.864**
									.000
PIV									1

DAS28: Disease Activity Score-28, VAS: Visual Analog Scale, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, RF: Rheumatoid factor, CCP: Citrullinated peptide antibody, SII: Systemic immune-inflammation index, SIRI: Systemic inflammation response index, PIV: Pan-immune-inflammation value, **. Correlation is significant at the 0.01 level (2-tailed), *. Correlation is significant at the 0.05 level (2-tailed).

DAS28-ESR. When patients were divided into three groups—remission, low, and high disease activity—it was observed that SII levels significantly increased with rising disease activity. The authors highlighted that, for the first time, SII demonstrated a stronger association with disease activity compared to NLR. Similarly, another study by Okutan and colleagues[19] reported that SII and PIV were significantly higher in RA patients compared to the control group, and these indices showed a positive correlation with the DAS28 score. Additionally, subgroup analyses based on disease activity revealed that SII had a significant predictive value for disease activity. The results of our study largely align with these two studies, with particular interest in emphasizing the predictive role of SII.

In our study, a moderate positive correlation was observed between CRP levels and SII. This finding suggests that SII may serve as an alternative inflammatory marker to CRP in the monitoring of RA. Indeed, in the study conducted by Dervisevic et al.,[20] SII values were significantly higher in RA patients compared to healthy individuals and showed positive correlations with hs-CRP (high sensitivity CRP), ESR, NLR, MLR, PLR, the number of tender joints, and the swollen-to-tender joint ratio. These results support the findings of our study and indicate that SII could be a meaningful tool reflecting the degree of inflammation in patients with RA.

According to current research, both SII and PIV levels were found to be lower in the group receiving anti-TNF-α therapy compared to those treated with DMARDs, suggesting that these two indices may serve as potential tools for evaluating treatment response. SII and PIV are not only associated with disease activity but may also be valuable indicators for assessing treatment effectiveness. It has been proposed that SII, alongside CRP and ESR, is an effective tool for monitoring response to TNF-α inhibitors in RA patients, with SII showing the highest predictive value among these markers for evaluating the efficacy of TNF-α inhibitors. However, in the retrospective study conducted by Bai et al,[21] PIV was not evaluated.In our study, PIV was also able to distinguish between the anti-TNF group and the DMARD group. When conventional treatments cause severe side effects or fail to achieve the desired clinical response, TNF-α inhibitors are considered alternative options for RA therapy. Widely used TNF-α inhibitors include infliximab, adalimumab, etanercept, golimumab, and certolizumab pegol, all of which aim to neutralize TNF-α and alleviate symptoms. In recent years, these agents have been shown to provide significant benefits in controlling disease activity and reducing treatment-related adverse effects.[22]

Using data from the National Health and Nutrition Examination Survey (NHANES) between 1999 and 2018, the relationship between SII and RA was investigated. A total of 37.604 individuals were included in the study, of whom 2.642 (7.03%) had an RA diagnosis. After adjusting for potential confounding variables, multivariate logistic regression analysis showed that higher SII levels were significantly associated with an increased risk of RA.[23]

Başaran and colleagues[24] investigated the association between disease activity and the levels of PIV and SII in patients with RA, aiming to determine which of these two inflammatory indices offers greater diagnostic utility. Their findings indicated that both PIV and SII levels were significantly higher in the active RA group compared to both the remission and control groups. PIV and SII levels were significantly higher in the remission group compared to the controls. In the ROC analysis for predicting remission, CRP did not show significant discriminatory ability. In contrast, both PIV and SII showed statistically significant results. Among them, PIV demonstrated higher sensitivity and specificity.[24]

In our study, a weak positive correlation was found between RF and SII, whereas a moderate positive correlation was observed between RF and PIV. It is well established that RF levels are associated with disease activity in patients with RA.[25] Moreover, fluctuations in RF titers are considered useful for monitoring both disease activity and treatment response.[26] Consistent with these findings, a positive correlation was also observed between DAS28 scores and RF levels. The associations between RF and both SII and PIV indicate that these inflammatory indices may serve as potential alternative markers for evaluating inflammatory status in RA.

No significant correlation was found between SIRI and DAS28 scores, nor was there a difference in SIRI levels between patients treated with DMARDs and those receiving anti-TNF therapy. In contrast, both PIV and SII showed significant associations with disease activity and treatment response. These findings suggest that PIV and SII are more reliable markers for monitoring RA, while the utility of SIRI appears limited.

Limitations

Our study has several limitations. We evaluated both newly diagnosed and long-term patients together. In general, most of the participants were patients receiving long-term treatment. Therefore, we were unable to assess the relationship between these markers and disease activity in patients with a shorter disease duration. The retrospective design of the study limited the ability to evaluate the prognostic significance of inflammatory indices and their utility in monitoring treatment response. Additionally, the single-center nature of the study and the relatively small sample size can also be considered as further limitations.

CONCLUSION

As a result, SII and PIV appear to be potential biomarkers capable of reflecting disease activity and monitoring treatment response in patients with RA. Notably, the sensitivity of SII to different levels of disease activity and the reduction of both indices with anti-TNF therapy highlight their clinical relevance and potential utility in practice.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Yozgat Bozok University Non-interventional Clinical Researches Ethics Committee (Date: 04.06.2025, Decision No: 2025-GOKAEK-2511_2025.06.04_526).

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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Review

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The critical role of early genetic diagnosis and phlebotomy treatment in preventing organ damage in hemochromatosis: modern diagnostic and therapeutic approaches

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ABSTRACT

Hemochromatosis, caused by the C282Y mutation in the HFE gene, is the most common inherited disorder of iron metabolism. Since there is no active iron excretion mechanism in the body, iron progressively accumulates in the liver, heart, pancreas and endocrine organs due to disorders in the hepcidin-ferroportin axis. The disease usually begins to show symptoms during the fifth decade of life, with the most common complaint being severe fatigue. If left untreated, hemochromatosis increases the risk of cirrhosis and hepatocellular carcinoma by around 20-fold. Transferrin saturation is considered together with ferritin elevation in diagnosis. Genetic testing targeting the HFE gene confirms the diagnosis and prevents unnecessary invasive interventions. In terms of measuring iron load in the liver, magnetic resonance imaging is the gold standard for non-invasive assessment. Therapeutic phlebotomy is still the cornerstone of treatment. Iron chelation therapy is the second option in cases where phlebotomy is contraindicated. Early diagnosis and treatment can prevent organ damage; however, late complications such as cirrhosis, hypogonadism, and arthropathy may be permanent. Hepcidin analogs and CRISPR technology are seen as promising treatment options in the future. With modern approaches, it is possible to detect the disease at an early stage and treat it effectively.

Keywords: Hereditary hemochromatosis, HFE gene mutation, phlebotomy, early diagnosis

INTRODUCTION

Hemochromatosis was first described as “bronze diabetes” by Armand Trousseau in 1865; later von Recklinghausen showed that this condition was associated with iron accumulation in the liver.[1,2] In 1935, Sheldon[3] demonstrated that the disease was a familial metabolic disorder. The first clue at the genetic level was identified in 1976 with the association with the HLA-A3 antigen,[4] and in 1996 it was shown that the C282Y mutation in the HFE gene was the main cause of the disease.[5] Today, as a result of these historical developments, hemochromatosis can be identified at an early stage through genetic tests, and periodic phlebotomy is an effective intervention that can prevent organ damage.[6]

Iron homeostasis is maintained by the balance between intestinal absorption, reticuloendothelial recycling, and limited physiological losses.[7,8] The reticuloendothelial system also supports iron levels by recovery from aging erythrocytes.[9] Losses through gastrointestinal epithelial turnover, dermal desquamation, and menstruation are minimal.[10] Since there is no active iron excretion mechanism in the body, systemic iron load is mainly regulated at the level of absorption via the hepcidin-ferroportin axis.[11] Disturbances in this regulatory system can cause a variety of clinical conditions ranging from iron deficiency anemia to iron overload syndromes such as hereditary hemochromatosis.[12] Hepcidin is a 25-amino acid peptide hormone synthesized in the liver and is the central regulator of this process.[11] Hepcidin binds to the ferroportin protein and withdraws iron transporters from intestinal enterocytes and macrophages, reducing absorption.[11] Hepcidin increases when iron stores are full (or in the presence of inflammation) and decreases in surgical blood loss, iron deficiency, or intensive erythropoiesis.[7]

Disruption in hepcidin levels constitutes the basic pathogenetic mechanism of hereditary hemochromatosis and other iron overload syndromes.[11] Mutations in the HFE, HJV, TFR2 and SLC40A1 genes either reduce hepcidin synthesis or prevent the action of hepcidin on ferroportin.[2] This leads to uncontrolled iron absorption from the intestines and excessive iron accumulation in the tissues. In cases of secondary hemochromatosis, hepcidin production is suppressed as a result of increased erythropoietic activity

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due to repeated erythrocyte transfusions (e.g. thalassemia intermedia) or impaired hepatocyte function in chronic hepatic diseases. As a result, hepcidin decreases, ferroportin activation continues and systemic iron accumulation occurs.[8]

ETIOLOGY

The cellular distribution of iron accumulation in primary and secondary hemochromatosis shows important differences in terms of diagnostics and clinical progression. Primary hemochromatosis is genetic and is characterized by systemic iron accumulation due to mutations. It is classically examined in four main types. The most common form, type 1 hereditary hemochromatosis, occurs in homozygous C282Y mutations of the HFE gene and shows autosomal recessive inheritance.[7] The H63D variant in the HFE gene has lower penetrance and usually contributes to the clinical picture in heterozygous combinations. Type 2 (juvenile) hemochromatosis, which is less common, is due to mutations in the HJV (hemojuvelin) or HAMP (hepcidin) genes and typically begins in adolescence.[13] Type 3 is due to mutations in the TFR2 (transferrin receptor 2) gene and is also inherited in an autosomal recessive manner.[14] In this variant, the disease may occur at an earlier age compared to cases with HFE mutations. Type 4 hemochromatosis is the only inherited form that is inherited in an autosomal dominant manner and is associated with mutations in the SLC40A1 gene.[15] This gene encodes the ferroportin protein, which transports iron out of the cell. The mutations in this type, which is often referred to as "ferroportin disease", lead to loss of ferroportin function or hepcidin resistance.

Secondary hemochromatosis develops due to acquired rather than genetic causes. The most common etiological factor is repeated erythrocyte transfusions due to diseases such as thalassemia major, sickle cell disease, and myelodysplastic syndrome.[16-18] Each erythrocyte unit contains approximately 200–250 mg of iron, which leads to systemic iron accumulation in the long term.[19] In addition, conditions with ineffective erythropoiesis (e.g. thalassemia intermedia) suppress hepcidin production, increase iron absorption from the intestines, and may lead to iron overload without transfusion.[20] Although rare, factors such as a high-iron diet, excessive oral iron intake, or consumption of iron-rich groundwater may also contribute to secondary iron overload.[21]

EPIDEMIOLOGY

Type 1 primary hemochromatosis is the most common autosomal recessive disorder of iron metabolism, especially in individuals of Northern and Western European descent. The homozygous form of the C282Y mutation in the HFE gene is seen in approximately 0.4–0.5% (1/200–1/250) of the populations in this region, while heterozygous carrier rate varies between 10–14%.[22] In contrast, non-HFE forms such as type 2 (juvenile), type 3 (TFR2-related), and type 4 (ferroportin disease) are quite rare; their prevalence varies between 1/100.000–1/1.000.000, and are frequently associated with isolated mutation clusters of Mediterranean, Middle Eastern, and Asian origin.[23]

Hereditary hemochromatosis due to the HFE gene is quite rare in Turkiye. In an epidemiological study, C282Y homozygous mutation was detected at a rate of 0.043% and heterozygosity at a rate of 2.5%. In the same study, H63D heterozygosity was detected in 24.1%, and it was reported that this variant was common but had low penetrance in the Turkish population.[24] Considering screening costs and the risk of creating "anxious healthy individuals", a national hemochromatosis screening program has not been implemented for the general population in any country. The optimal strategy today is targeted screening.

Sex is an important variable affecting clinical presentation. In women, menstrual blood loss can physiologically regulate iron balance among affected individuals, while in men, iron accumulation becomes symptomatic at an earlier age. Hereditary hemochromatosis is approximately 2–3 times more common in men than in women.[25]

PATHOPHYSIOLOGY

The Pathophysiology of Primary Hemochromatosis

The basic pathophysiological mechanism of primary hemochromatosis is the disruption of the hepcidin-ferroportin axis, which regulates systemic iron homeostasis. Under normal conditions, hepcidin, which is synthesized in hepatocytes, controls iron release from enterocytes and reticuloendothelial macrophages in the intestinal epithelium. Hepcidin interacts with ferroportin, allowing this protein to be removed from the cell membrane.[26] The C282Y mutation in the HFE gene reduces hepcidin production, leading to increased absorption of iron from the duodenum and uncontrolled release of iron from macrophages. This elevation overwhelms transferrin, resulting in non-transferrin-bound iron (NTBI) in the plasma.[27] Cellular damage caused by iron accumulation develops through the interaction of multiple pathophysiological mechanisms. These include oxidative stress, ferroptosis, inflammatory activation, hormonal dysfunction and immune suppression.[28] Increased reactive oxygen species cause damage to cell membranes, proteins and DNA. Ferroptosis is an important damage pathway especially in the liver and heart.[29]

The Pathophysiology of Secondary Hemochromatosis

Unlike hereditary forms, secondary hemochromatosis develops due to excessive iron intake or impaired erythrocyte turnover. The most common cause is repeated red blood cell transfusions in diseases such as thalassemia major, sickle cell disease or myelodysplastic syndrome.[16-18] The excess leads to accumulation of free iron (NTBI) and parenchymal organ damage. Another secondary loading mechanism is erythropoietic hemochromatosis, characterized by chronic erythropoietic stress and ineffective erythropoiesis. Ineffective erythropoiesis and chronic erythropoietin stimulation suppress hepcidin levels and increase intestinal iron absorption.[19]

Organ-Based Pathophysiological Effects

Although similar organ systems may be affected in primary and secondary hemochromatosis, the site of iron accumulation and the severity of damage are different. In the primary form, iron accumulates directly in parenchymal tissues such as the liver, pancreas, heart and endocrine organs, leading to severe damage in these tissues and a higher-paced progression.[30] In secondary hemochromatosis, iron is

primarily stored in the reticuloendothelial system (spleen, bone marrow, Kupffer cells). Parenchymal involvement develops later and is usually milder.[31]

Accumulation in hepatocytes eventually triggers fibrosis and micronodular cirrhosis. This process dramatically increases the risk of HCC. In some cohorts, the risk of HCC has been reported to be 20 times higher than in the general population.[32] The risk of developing cirrhosis is approximately 9-fold higher in individuals with HFE mutations.[33] Impairment of β-cell functions in the pancreas leads to decreased insulin secretion and the development of diabetes mellitus in around 40–50% of individuals with the homozygous C282Y mutation.[34] Iron overload not only reduces insulin secretion, but also increases insulin resistance. Pathological accumulation of iron in the heart tissue can lead to myocardial fibrosis, decreased contractility, and electrical conduction disorders.[35] Joint involvement leads to arthropathy that mimics degenerative joint diseases, but with calcium pyrophosphate dihydrate (CPPD) crystals in the synovial fluid.[36] Iron accumulation can lead to hormonal dysfunction in the pituitary, gonad, thyroid and pancreas. The most common endocrine disorder is hypogonadism, which can manifest with loss of libido, infertility, and amenorrhea.[37] Thyroid involvement can result in hypothyroidism.[38] More rarely, adrenal and parathyroid involvement can cause hypocortisolism or hypoparathyroidism.

DIAGNOSIS AND CLINICAL FINDINGS

Patients with hereditary hemochromatosis usually do not manifest with overt symptoms until middle age. Even if present at an early stage, the symptoms are not specific; most patients may live for years with only complaints such as chronic fatigue (70% of cases), weakness, and joint pain.[39] Due to these non-specific symptoms, diagnosis is often delayed, increasing the risks for organ damage. While the disease manifests in the fifth or sixth decade of life, in women, symptoms may be delayed due to regular blood/iron loss with menstruation.[40] The disease can be diagnosed at an earlier stage if there is a family history or if high ferritin/transferrin saturation is detected in routine blood tests.

Most patients develop hepatomegaly and high liver enzymes, especially in advanced cases.[41] Jaundice is usually absent in the early stage, but may occur in advanced disease. Abdominal pain, tenderness in the right upper quadrant, hepatomegaly and splenomegaly are common findings. Cirrhosis may develop in the long term.[42] When cirrhosis occurs, prognosis is worsened and the risk of developing HCC increases greatly. It has been reported that the lifetime probability of developing HCC can reach 20% in patients with hemochromatosis.[43]

Excessive iron may accumulate in the pancreas, especially in the islets of Langerhans, leading to the development of diabetes. Diabetes prevalence in patients with hemochromatosis varies between 20–50%,[34] which is particularly high in individuals with advanced liver involvement. Regular phlebotomy treatment can improve blood sugar control even after diabetes develops; however, insulin requirement may continue in advanced cases.[44]

Hyperpigmentation is an early and common symptom of hemochromatosis. This bronze discoloration, observed in 70% of patients, is especially evident in the face and arm areas exposed to the sun and is due to increased melanin and dermal iron accumulation.[45] Dryness, thinning, ichthyosiform rashes on the skin, and hair loss throughout the body, especially in the pubic region, may be observed. Spoon nails are a characteristic dermatological finding, especially seen on the thumb and index finger, and are detected in approximately half of patients with hemochromatosis.[46]

Hemochromatosis can lead to a specific arthropathy due to the accumulation of calcium pyrophosphate crystals in the joints and chondrocalcinosis, which is especially evident in the 2nd and 3rd metacarpophalangeal joints. This condition, which clinically mimics osteoarthritis, can affect large joints such as the knee, hip, and spine, in addition to the hand joints. Joint complaints, unlike many other findings of hemochromatosis, usually do not regress with treatment and may be permanent.[47] Chronic iron accumulation and decreased bone mineral density due to hypogonadism are frequently seen in patients with hemochromatosis; therefore, bone mineral density studies are recommended, especially in individuals older than 40 years.[48]

Dilated or restrictive cardiomyopathy in the heart muscle may also be observed, and might present with shortness of breath, edema, arrhythmia, and conduction disorders.[49] Cardiomyopathy due to hemochromatosis may be the first symptom in young patients, and in some series, 15% of cases were found to manifest with cardiac symptoms.[50] While phlebotomy treatment initiated early can partially reverse cardiac impact, the damage becomes permanent in the late period.

Iron accumulation can cause hypogonadism, diabetes, and hypothyroidism. The most common endocrine complication is hypogonadotropic hypogonadism of pituitary origin. It progresses with loss of libido, erectile dysfunction, and gynecomastia in men, while females present with menstrual irregularities. Testicular involvement can also cause primary hypogonadism.[51] Thyroid involvement increases the risk of hypothyroidism, while adrenal and parathyroid involvement are rare.

Osteoporosis is also a common problem in patients with hemochromatosis. Approximately one quarter of patients have significant osteoporosis and more than 40% have osteopenia.[52] This decrease in bone density is associated with hypogonadism and high iron overload, and when necessary, treatments that protect bone health should be planned.

The accumulation of iron in macrophages restricts anti-pathogen activity. The risk of infection against siderophilic bacteria increases in individuals with hemochromatosis.[53] In particular, pathogens such as *Vibrio vulnificus*, *Listeria monocytogenes* and *Yersinia enterocolitica* can multiply rapidly in iron overload.[54] Since *V. vulnificus* infections can be fatal after consumption of raw seafood, it is recommended to avoid these foods.[55]

Hemochromatosis can rarely affect the central nervous system and cause movement disorders such as chorea or tremor as a result of iron accumulation in the basal ganglia. Evidence for these impacts usually come from case reports, and therefore, it is evident that neurological complications are rare and most patients do not develop significant central nervous system involvement.[56]

Hemochromatosis can be confused with many clinical conditions, especially in patients presenting with elevated ferritin. Secondary causes of hemochromatosis (e.g. chronic transfusions, hemolytic anemias, ineffective erythropoiesis) should be distinguished from the primary form. In addition, conditions such as viral hepatitis (especially HCV), MASLD, alcoholic liver disease, and dysmetabolic hyperferritinemia can also increase ferritin levels.[57] Transferrin saturation is usually normal in these cases. Iron parameters, genetic tests, clinical history, and concomitant disease findings should be evaluated together for diagnosis.

LABORATORY FINDINGS

In case of suspected hereditary hemochromatosis, the first evaluation is made with serum transferrin saturation and ferritin levels. Transferrin saturation exceeding 50% in men and 40% in women suggests iron overload.[48] EASL guidelines accept a transferrin saturation above 45% as being indicative of hereditary hemochromatosis.[43] This threshold value can capture 97.9-100% of individuals with C282Y homozygous mutation.[58] Transferrin saturation is not always reliable in assessing iron accumulation in secondary hemochromatosis. Therefore, it should be evaluated together with ferritin levels and, if necessary, tissue iron measurements.

While ferritin is a biomarker reflecting intracellular iron stores, it is also an acute phase reactant. Therefore, ferritin levels may increase independently of iron overload in conditions such as inflammation, infection, liver diseases, malignancies and metabolic disorders. In the literature, it has been reported that only approximately 10% of patients with elevated ferritin levels have true iron overload.[6] Transferrin saturation below 45% and serum ferritin within the normal range have a negative predictive value of approximately 97% in excluding the possibility of significant iron overload.[40] Ferritin >300 µg/L in men and >200 µg/L in women and concurrent high transferrin saturation are suggestive of hereditary hemochromatosis and may necessitate genetic testing.[43]

In hemochromatosis, mild increases in ALT and AST levels are usually seen due to liver iron accumulation. These increases usually do not exceed 2 times the normal level.[57] It is notable that enzyme levels may further increase in advanced stages of the disease, especially with fibrosis or cirrhosis.[21] In adults with unexplained and persistent mild transaminase elevation, screening for hemochromatosis is recommended.

Owing to the impact of hemochromatosis on the pancreas and glucose intolerance, screening for diabetes is recommended in individuals suspected of having hemochromatosis. Erythrocyte lifespan may be shortened in patients with hemochromatosis due to hemolytic processes or frequent phlebotomy applications. This causes HbA1c to underestimate the mean glucose level.[59] Therefore, HbA1c may not be reliable in the diagnosis and follow-up of diabetes in individuals with hereditary hemochromatosis. It may be beneficial to prioritize direct measurement methods such as fasting glucose, fructosamine test and OGTT in this patient population.[60]

HFE gene mutation analysis is the basic confirmatory test for the diagnosis of hereditary hemochromatosis. The C282Y mutation is the most common cause, especially in individuals of Northern European origin, and is detected in homozygous form in more than 80% of cases.[61] The second most common mutation, H63D, usually contributes to the disease in the form of combined heterozygosity with C282Y. For this reason, it is recommended to perform HFE genetic testing in patients with high transferrin saturation and/or ferritin and to investigate C282Y and H63D mutations.[62] Detection of HFE mutation confirms the diagnosis of hereditary hemochromatosis, thus avoiding unnecessary advanced invasive procedures (such as liver biopsy). If there are no HFE mutations but clinical findings are strong, advanced analysis for rare genes such as TFR2, HAMP, HJV, and SLC40A1 can be considered.[23] However, in the adult population, diagnosis can be made only with the HFE test in >90% of cases.[63]

Hormonal evaluation should be performed in patients with high ferritin or iron overload. In men, morning total testosterone and LH/FSH levels should be checked; in women, menstrual status should be questioned and pituitary-gonadal axis tests should be performed if necessary. If there is clinical suspicion, thyroid function tests, fasting glucose and HbA1c should be added to the evaluation.

IMAGING MODALITIES

Magnetic resonance imaging (MRI) is the reference imaging method for quantitative and non-invasive evaluation of liver iron accumulation, especially since it avoids the need for invasive biopsy. Accumulation in organs such as the heart, pancreas and pituitary gland can also be detected.[64] MRI is used to determine the severity of iron accumulation even in genetically-diagnosed hereditary hemochromatosis and helps predict the risk of organ damage.[65] High iron accumulation in the liver and low iron accumulation in the spleen suggests primary hemochromatosis; accumulation in the spleen supports secondary causes.[66]

Echocardiography is the first-line imaging method for the evaluation of iron-related cardiomyopathies (dilated/restrictive) in hemochromatosis. The EASL 2022 guideline recommends that all patients with severe hemochromatosis who have symptoms of heart disease should undergo transthoracic echocardiography together with an ECG and, if necessary, support it with cardiac MRI (T2-MRI).[48] Cardiac MRI (T2-MRI) is important for early diagnosis and intervention, especially in juvenile cases.[67] Treatment initiated with early diagnosis can partially reverse cardiac dysfunction. Chest radiography may also provide supportive evidence for advanced heart failure findings.

Liver biopsy has been considered the "gold standard" for measuring liver iron in hemochromatosis for many years and is also considered the most sensitive method for determining the degree of tissue damage caused by iron.[68] Histological examination of liver tissue with Perls Prussian blue staining shows a classic iron distribution in hereditary hemochromatosis. Iron accumulation is seen predominantly in hepatocytes and also in bile duct epithelial cells, with minimal presence in some reticuloendothelial elements (e.g., Kupffer cells). This parenchymal iron accumulation pattern is typical of most cases of hereditary hemochromatosis and helps distinguish it from secondary iron overload.[69] In cases of transfusion-related hemosiderosis or chronic hemolytic anemia, iron accumulation occurs primarily in Kupffer cells, with limited involvement of hepatocytes. Thus, the presence

of iron primarily in hepatocytes on liver biopsy supports the hereditary form, whereas excessive iron in macrophages suggests secondary causes.[31]

The 2011 AASLD guideline recommended liver biopsy to assess the risk of cirrhosis in patients with hereditary hemochromatosis who have serum ferritin >1000 µg/L or elevated liver enzymes.[57] The EASL 2022 guideline recommends non-invasive methods such as transient elastography (Fibroscan), FIB-4 and APRI instead of routine biopsy.[48] In patients with very high ferritin levels, the degree of liver fibrosis is first investigated with these non-invasive tests. If advanced fibrosis/cirrhosis cannot be definitely excluded with non-invasive methods or if the results are contradictory, biopsy is indicated.[48] In modern management, liver biopsy is reserved for cases where the diagnosis of cirrhosis cannot be confirmed with clinical and non-invasive tests. The iron concentration and fibrosis score (e.g. METAVIR) obtained with biopsy are still valuable in determining the stage of the disease.[70]

Ferritin, transferrin saturation and/or HFE genetic testing is recommended for first-degree relatives of individuals diagnosed with hereditary hemochromatosis. The ACG, AASLD and EASL guidelines recommend genetic counseling and family screening.[40,48,57]

TREATMENT

The main treatment for primary hemochromatosis is regular therapeutic phlebotomy. Phlebotomy gradually depletes iron stores by removal of blood at intervals; this method is usually easy, cheap and extremely effective. During the induction phase, 450–500 ml of blood is taken at weekly intervals to reduce the ferritin level to ~50 µg/L. This level is then maintained with less frequent phlebotomies during the maintenance period (once a month or every few months).[71] In patients with high iron overload, it may take months to reach the target, and dozens of phlebotomies may be required.[72] Appropriately initiated early treatment is effective in preventing complications such as cirrhosis and HCC. Significant improvements in findings such as hyperpigmentation, insulin resistance and fatigue can be achieved with phlebotomy. However, advanced complications such as cirrhosis, hypogonadism, and arthropathy are often irreversible.[73]

Erythrocyte apheresis is an iron-reducing treatment method applied by selectively removing erythrocytes from peripheral blood and returning plasma, improving tolerability. Randomized controlled trials have shown that this method reduces serum ferritin levels more rapidly than conventional phlebotomy and reduces the total number of sessions.[74] In addition, in cases that do not respond to phlebotomy, erythrocyte apheresis combined with low-dose erythropoietin can be applied.[74]

Iron chelation is performed with drugs that chemically bind and remove accumulated iron in the body. This is a second-line treatment option, especially in cases of primary hemochromatosis where phlebotomy is contraindicated or intolerable.[40,72] In addition, in cases of secondary hemochromatosis due to transfusions (e.g. thalassemia major), chelation is the primary treatment method since phlebotomy cannot be applied.[75] Chelators such as deferoxamine (i.v./s.c.), deferasirox (oral), and deferiprone (oral) bind iron and increase its excretion via urine or feces. Due to potential toxicities, treatment should be carried out in experienced centers and with close biochemical monitoring.

Liver transplantation should be considered in patients with hemochromatosis who develop advanced fibrosis, cirrhosis, or HCC. Current data show that transplantation outcomes have improved significantly in this group. In a study covering the period 2003–2019, it was reported that 1- and 5-year survival rates in patients who underwent liver transplantation due to hereditary hemochromatosis were similar to the general transplant patient population.[76] Since the risk of HCC continues in the presence of advanced fibrosis or cirrhosis, screening with ultrasonography and AFP levels should be performed throughout life.

Hepcidin-based treatments (e.g. Rusfertide/PTG-300) and oral ferroportin inhibitors have emerged as alternative pharmacological options to phlebotomy in recent years. Hepcidin analogs have been shown to lower iron parameters and reduce the need for phlebotomy in phase 2 studies.[77] With genetic engineering approaches such as CRISPR/Cas9, HFE gene mutations have been successfully corrected in mouse models, with success in reducing iron accumulation in the liver.[78] Although these strategies have the potential for permanent treatment in the future, they have not yet been put into clinical practice. Currently, phlebotomy remains the standard treatment.

If left untreated, hemochromatosis can lead to progressive organ damage and serious complications such as cirrhosis and HCC. The main factors that determine prognosis are the presence of cirrhosis at the time of diagnosis, high ferritin levels, male sex, advanced age, alcohol use and concomitant metabolic diseases.[79] In patients diagnosed and treated at an early stage, the life expectancy is similar to healthy individuals; however, the risk of HCC and mortality is significantly increased in those presenting with cirrhosis. Therefore, iron-reducing treatment should be continued even in cirrhotic patients and regular HCC screening should be performed.[48]

CONCLUSION

Taken together, treatment of hemochromatosis is not limited to phlebotomy alone, but requires a holistic approach that includes patient education, lifestyle changes, and multidisciplinary follow-up.

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Referee Evaluation Process

Externally peer-reviewed.

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The authors have no conflicts of interest to declare.

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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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Case Report

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A case developing *Candida auris* related candidaemia following multiple drug-resistant *Klebsiella pneumoniae* meningitis after neurosurgical intervention

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ABSTRACT

A 28-year-old man who underwent ventriculoperitoneal shunt (VPS) operation at another medical center due to epidural abscess and hydrocephalus was admitted due to deterioration of his general condition. He was receiving vancomycin and meropenem treatment for epidural abscess. Urine cultures were taken during hospitalization and again 48 hours later and *Candida auris* (*C. auris*) growth of 10^5cfu/ml was detected. On the 4th day of hospitalization, the patient was intubated due to decreased oxygen saturation, and while under meropenem and vancomycin treatment, carbapenem-resistant, gentamicin and ceftazidime-avibactam-susceptible and multidrug-resistant *Klebsiella pneumoniae (K. pneumoniae)* growth was detected in CSF culture. The patient's VPS was removed and hydrocephalus was followed with extra-ventricular drainage (EVD). Vancomycin treatment was discontinued and intrathecal (IT) gentamicin treatment was started. Due to the susceptibility of *K. pneumoniae* growth from deep tracheal aspirate to ceftazidime-avibactam, antibiotic treatment was changed to intravenous (IV) meropenem, IV ceftazidime-avibactam and IT gentamicin and treatment was continued for 10 days. On the 20th day of hospitalization due to deterioration of his clinical condition under treatment, tracheostomy was performed, he was intubated, blood and urine cultures were repeated and *C. auris* growth was detected in blood culture on the 27th day after hospitalization using VITEK MS MALDITOF (bioMérieux, France) microbiological identification system. Confirmation of the *C. auris* species and antifungal susceptibility testing was performed by the Mycology Reference Laboratory, Institute of Public Health and antibiotic treatment was stopped. According to the antifungal susceptibility test results, the patient was started on anidulafungin. In conclusion, nosocomial *C. auris* infection should be considered in patients with underlying predisposing factors such as long intensive care unit stays, broad-spectrum antibiotic use, surgical interventions, central venous catheter use, intubation and infection due to gram-negative bacteria.

Keywords: Nosocomial meningitis, multidrug-resistant, *Klebsiella pneumoniae*, *Candida auris*, candidemia

INTRODUCTION

Post-neurosurgical meningitis (PNM), a complication with a high mortality rate, may develop after neurosurgical interventions. The most common bacteria causing PNM are *Acinetobacter baumannii* and *Klebsiella pneumoniae (K. pneumoniae)*.[1] PNM due to multidrug-resistant (MDR) *K. pneumoniae* has a high mortality rate if not treated appropriately.[2]

In recent years, cases of nosocomial *Candida auris* (*C. auris*) have been reported in patients hospitalized in intensive care units (ICUs) with underlying predisposing factors.[3-6] *C. auris* is an important *Candida* species that can show multiple antifungal resistance and is frequently identified by molecular methods.[7-10] In this article, we report a 28-year-old male patient who developed fungemia and candiduria due to *C. auris* following meningitis due to MDR *K. pneumoniae* after neurosurgical surgery.

CASE

A 28-year-old male patient who underwent ventriculoperitoneal shunting (VPS) due to epidural abscess and hydrocephalus

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in another healthcare institution was admitted to the ICU of brain and nerve surgery due to deterioration in general condition. It was learned from his epicrisis that he had been operated on three years ago for subdural hematoma and underwent cranioplasty. It was learned from his epicrisis that he was operated on for right parenchymal hematoma in the brain after a motor vehicle accident approximately 2 years after this operation, and VPS was performed in another healthcare institution due to the development of hydrocephalus, and vancomycin and meropenem treatment was administered for 30 days. On physical examination at the time of admission to the ICU of brain and nerve surgery, the general condition was moderate, consciousness was blurred, the Glasgow coma score was 12, the patient was extubated, and the patient was receiving oxygen therapy with a mask due to respiratory distress. Pupils were isochoric, and light reflex was present. The patient had left hemiplegia and a stage 2 sacral decubitus ulcer. Laboratory tests revealed a leukocyte count of 9360/mm^3, C-reactive protein (CRP) of 54 mg/L (normal <5 mg/L), a glomerular filtration rate of 150 ml/min, and other laboratory tests were normal. The patient was consulted in the infectious diseases department in the brain and nerve surgery ICU, and treatment with vancomycin and meropenem was continued. Urine culture taken on the day of hospitalization showed >10^5 cfu/ml *C. auris* growth after 48 hours, and there was no significant growth in blood and catheter cultures. On the 4th day of hospitalization, the patient was intubated due to decreased oxygen saturation (SpO_2<75). Blood, intracatheter blood, cerebrospinal fluid (CSF), and rectal swab cultures were obtained from the patient whose CRP value was found to be increased. There was no growth in blood and intracatheter blood cultures. Vancomycin-resistant enterococci (VRE) were grown in the rectal swab sample, and contact isolation measures were applied. While under meropenem and vancomycin treatment, carbapenem-resistant, MDR *K. pneumoniae* susceptible to gentamicin and ceftazidime-avibactam was grown in CSF culture. VPS was removed, and hydrocephalus continued to be monitored with extra ventricular drainage (EVD). Vancomycin treatment was discontinued, and IT gentamicin treatment was started. Upon the growth of *K. pneumoniae* susceptible to ceftazidime-avibactam in deep tracheal aspirate culture, the patient's treatment was adjusted to meropenem intravenous (IV), ceftazidime-avibactam (IV), and gentamicin IT. Treatment was administered for 10 days. There was no growth in the CSF culture obtained under treatment, the cell count in CSF was normal, and the patient's EVD was withdrawn. On the 20th day of hospitalization, the patient's clinical findings worsened under treatment, tracheostomy was opened, and the patient was intubated; blood and urine cultures were repeated. *C. auris* was grown in the urine culture obtained during hospitalization and in the blood culture obtained on the 27th day of hospitalization. *C. auris* grown in urine culture was not considered an infectious agent. *C. auris* grown in blood culture was identified by the VITEK® MS MALDI-TOF (BioMérieux, France) microbiologic identification system. Confirmation of the *C. auris* strain grown in blood culture and antifungal susceptibility tests were performed by Mycology Reference Laboratory. Existing antibiotic treatments were discontinued. Susceptibilities of *C.auris* strains to amphotericin B, azoles (fluconazole, itraconazole, voriconazole, posaconazole), and echinocandins (anidulafungin, micafungin, caspofungin) were studied by liquid microdilution according to CLSI M27-A3. MIC values obtained as a result of the antifungal susceptibility study of the strain isolated from blood; amphotericin B: 1 (µg/ml), voriconazole: 0.25 (µg/ml), caspofungin: 0.5 (µg/ml), posaconazole: 0.5 (µg/ml), fluconazole: 256 (µg/ml), itraconazole: 0.5 (µg/ml), anidulafungin: 1(µg/ ml). Anidulafungin treatment was started according to the antifungal susceptibility results. The patient's medical devices were separated, contact isolation measures and infection control measures were applied. Following the treatment, daptomycin was added to the patient's treatment with the diagnosis of catheter infection due to the growth of *Staphylococcus haemolyticus* in blood and intracatheter blood cultures. Anidulafungin and daptomycin treatment was administered for 14 days, and the central venous catheter was withdrawn. After treatment, the patient's general condition improved, and he was transferred from the ICU to the brain and nerve surgery service. No pathologic findings developed except for left hemiplegia, which was detected at the beginning. The patient was discharged for follow-up.

DISCUSSION

PNM is an important and life-threatening complication of neurosurgical operations. The most frequently reported PNM agents in the literature are *Acinetobacter baumannii* and *K. pneumoniae*.[1,2] Iaria et al.[1] evaluated the results of intraventricular colistin treatment in five patients who developed PNM due to MDR gram-negative bacteria in a study conducted in Italy. In the study, MDR *Acinetobacter baumannii* and MDR *K. pneumoniae* were isolated in four and one case, respectively. Intraventricular colistin treatment was administered for a median of 18 days, and IV meropenem and colistin treatment was administered together with intraventricular colistin in all cases. Four of the patients recovered with treatment and were discharged, while one patient died as a result of respiratory complications. Patrial et al.[2] also reported two cases of PNM due to carbapenem-resistant *K. pneumoniae*. In these cases, it was reported that *K. pneumoniae* strains had extended-spectrum beta-lactamase enzymes together with KPC enzymes responsible for carbapenem resistance. The cases were successfully treated with IT polymyxin B followed by I.V. meropenem therapy. Sreejith et al.[11] reported a 26-year-old male patient who developed pneumocephalus as a complication of meningitis due to MDR *K. pneumoniae* as a complication of chronic suppurative otitis media.

In the present case, MDR *K. pneumoniae* was isolated as the causative agent of PNM. Since the isolated strain was susceptible to gentamicin, IT gentamicin and meropenem treatment was started by the IV route. After 10 days of treatment, there was no growth in CSF culture. In the present case, *C. auris* was grown in the urine culture obtained during hospitalization and in the blood culture obtained on the 27th day of hospitalization.

Our case is interesting because it is the first case of candidiasis due to *C. auris* following PNM due to MDR *K. pneumoniae* and the first case of *C. auris* reported in our hospital. According to the English literature, our case is the first case of *C. auris* infection following PNM due to *K. pneumoniae*. *C. auris* is a hospital-acquired *Candida* species

that has been the focus of attention in the world and Turkiye in recent years. *C. auris* was first reported in 2009.[6] *C. auris* is an important opportunistic pathogen because it causes outbreaks as well as nosocomial infections, is resistant to antifungals and disinfectants, and cannot be identified by current conventional identification systems.[3,5,12]

The fact that *C. auris* can easily spread among patients and between hospitals, cause epidemics, survive on surfaces for a long time, and show multiple antifungal drug resistance has caused concern all over the world.[3,5,12,13] Garcia et al.[12] reported an outbreak due to *C. auris* between 2017 and 2019 in their study conducted in Spain. In the study, it was reported that a total of 203 patients were colonized or infected with *C. auris*, and invasive *C. auris* infection developed in 30 patients (candidemia in 29 cases and meningitis in one case). The causative agent was determined to be *C. auris* in 32% of cases with candidemia, and all *C. auris* isolates were fluconazole resistant. In the *C. auris* strain isolated in the present study, high fluconazole minimal inhibitory concentration (MIC) values (≥256 mg/ml) were found, while MIC values for other antifungals were low.

In the literature, it has been reported that 60-90% of *C. auris* strains are resistant to fluconazole, 10-30% have high minimum inhibitory concentration values for amphotericin B, and approximately 5% are resistant to echinocandins.[13] Today, outbreaks due to *C. auris* have been reported in hospitals in many countries.[4,12] Thoma et al.[5] reported an outbreak due to carbapenem-resistant MDR *A. baumannii* and *C. auris* in the COVID-19 pandemic. In the study, lack of personal protective equipment, hand hygiene, and use of personal protective equipment were reported as the most frequently reported potentially modifiable factors contributing to outbreaks. Bölükbaşı et al.[4] reported a 71-year-old male patient with underlying lung cancer and diabetes who developed fungemia due to *C. auris* after COVID-19 infection.

The patient was started on immunosuppressive corticosteroid and tocilizumab treatments for COVID-19 pneumonia. The *Candida* strain grown in the patient's blood culture was identified as *C. auris* by the VITEK MS MALDI-TOF system and confirmed by sequence analysis. The isolated *C. auris* strain was fluconazole resistant and susceptible to amphotericin B, anidulafungin, caspofungin, itraconazole, and posaconazole. Despite caspofungin and broad-spectrum antibiotic treatment, the patient died on the ninth day of treatment. Based on this case, the authors recommended caution in terms of *C. auris* infections, especially in ICUs. The main reasons for the increase in *Candida* infections are the increase in the number of immunosuppressive patients, the use of broad-spectrum antibiotics, and the widespread use of invasive interventions (central venous catheter, urinary catheter, tracheostomy, etc.).[6,14]

Broad-spectrum antibiotic use, immunosuppressive agents, and catheterization are among the predisposing factors for *C. auris* infection.[5,6] Kömeç et al.[6] reported a *C. auris*-related infection in three patients hospitalized in the ICU in İstanbul. The common features of the three cases reported were that they were ICU intubated patients, they had central venous catheters, they used broad-spectrum antibiotics, and they were reported as infections due to MDR bacteria. In all seven cases of *C. auris* reported from the United States, hematologic malignancy, bone marrow transplantation, central venous catheterization, and urinary catheterization were reported as predisposing factors.[6,16] In our case, the main risk factors were the use of broad-spectrum antibiotics, meningitis due to MDR *K. pneumoniae*, the presence of a urinary catheter, a central venous catheter, EVD, and the patient being ventilator dependent. Automated systems used in routine diagnosis are insufficient in identifying *C. auris* or may lead to erroneous definitions.[6,13]

The three isolates identified as *C. auris* by Kömeç et al.[6] by MALDI-TOF Microflex LT/SH Smart MS were confirmed by conventional methods and DNA sequence analysis at the National Mycology Reference Laboratory. By the liquid microdilution method, all three isolates were reported to be fluconazole resistant (MIC) values (>256 mg/ml). *C. auris* can cause nosocomial infections and outbreaks because it can survive for a long time in hospital environments. Therefore, *C. auris* is of nosocomial origin.[3,4] In addition, the fact that it can colonize on the skin and is resistant to disinfectants facilitates its spread. Its high rate of resistance to antifungal drugs leads to treatment failures.[4,13] With the case we presented, we aimed to draw attention to the infections caused by *C. auris*, its diagnosis, and risk factors. *C. auris* can be erroneously identified by routine laboratory methods, the VITEK-2 automated system, and API systems. Therefore, confirmation of *Candida* isolates by MALDI-TOF MS or DNA sequence analysis is recommended.[6,7,15] In our case, *C. auris* was identified by VITEK® MS MALDI-TOF (BioMérieux, France) and confirmed by DNA sequence analysis at the Public Health Mycology Reference Laboratory.

Karabıçak et al.[7] found fluconazole resistance in 70 *C. auris* isolates isolated from various hospitals in Turkiye (MIC50 and MIC 90 ≥256mg/ml) by the liquid microdilution method, while the identification of the isolates was identified by MALDI-TOF MS, and the sequence analysis of the isolates was 100% compatible with *C. auris*. Kulaklı et al.[8] reported *C. auris* in tissue culture in a 59-year-old male patient who underwent below-knee amputation due to diabetic foot infection. *C. auris* was identified by MALDI-TOF MS. The MIC value of *C. auris* isolate was reported as >64 µg/ml for fluconazole, 2 µg/ml for amphotericin B and 0.25 µg/ml for caspofungin. It was reported that the case was the first case of *C. auris* reported from İzmir province, and there was no growth in the culture performed again from the amputation site after antifungal treatment. Patient-directed infection control measures were taken to prevent interpatient transmission. In the present case, the patient's medical instruments were separated, contact isolation was performed, and infection control measures were taken. Aslan et al.[9] isolated *C. auris* from urine and blood cultures in an 89-year-old female patient receiving treatment for ventilator-associated pneumonia in ICU. The isolated *C. auris* was identified by MALDI-TOF MS and confirmed by sequence analysis. When fluconazole MIC value was found to be 16 mg/ml in the *C. auris* isolate, amphotericin B treatment was started according to the antifungal susceptibility result, contact isolation was performed, and infection control measures were taken. Öncel et al.[10] reported that 10 (6.3%) of a total of 157 *Candida* spp. isolated from ICU inpatients were *C. auris* in their study conducted in İstanbul. The most frequently isolated *Candida* species was reported as *Candida albicans* with 60 (38.2%) isolates. In the study, it was reported

that *C. auris* strains had high MIC values for amphotericin B, fluconazole, itraconazole, voriconazole, and posaconazole by the liquid microdilution method and showed multidrug resistance.

Özalp et al.[17] reported the *Candida* species isolated from a total of 217 patients in their retrospective study investigating *Candida* species causing bloodstream infections between 2020 and 2011 as *Candida albicans* 37.8%, *C. parapsilosis* 17.1%, *C. glabrata* 15.2%, *C. tropicalis* 15.2% and *C. auris* 9%, respectively. Candidemia developed in 175 (81.4%) patients during hospitalization in the ICU. Mortality was reported in 114 (52.3%) patients in the study group, and mortality rates were lower in patients infected with *C. parapsilosis* or *C. auris*. Age and previous COVID-19 infection were identified as risk factors for candidemia.

The 2022 SENTRY Antifungal Surveillance Program has been reported a significant increase in the prevalence of *C. auris* among invasive candidiasis isolates compared to previous years (≤0.1% before 2018, 0.4%-0.6% from 2018 to 2021 and 1.6% in 2022). The study included 28 (35.9%) *C. auris* isolates from the USA, 26 (33.3%) from Panama, and 12 and 9 isolates from Greece and Turkiye, respectively. Of all isolates, 82.1% were resistant to fluconazole, 17.9% to amphotericin B and 1.3% to caspofungin, anidulafungin or micafungin. Pan-drug resistance has not observed, but 17.9% of isolates were reported to be resistant to fluconazole and amphotericin B.

CONCLUSION

As a result, it should be kept in mind that nosocomial *C. auris* infection may be seen in patients with predisposing factors such as long-term hospitalization in the ICU, underlying broad-spectrum antibiotic use, surgical intervention, central venous catheter use, intubation, and infection due to MDR gram-negative bacteria.

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 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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Ankyra Medical Journal

Case Report

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Ocular manifestations of atypical hemolytic uremic syndrome: a case report

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ABSTRACT

Atypical hemolytic uremic syndrome (aHUS) is a rare but serious condition that is often associated with renal impairment and thrombotic microangiopathy. This case report presents the case of a 20-year-old female with a long-standing diagnosis of aHUS who developed hypertensive choroidopathy, a rare ocular manifestation. The patient presented with sudden-onset hypertension and visual disturbances, with a blood pressure of 270/120 mmHg. Ophthalmological examination revealed bilateral papilledema, Elschnig spots, and Siegrist streaks, indicative of hypertensive choroidopathy. Imaging studies, including fundus photography, fluorescein angiography, and optical coherence tomography (OCT), confirmed retinal findings and optic disc edema. This case emphasizes the critical need for early detection and regular ophthalmological monitoring in aHUS patients, as ocular changes, such as hypertensive choroidopathy, can be early indicators of systemic complications. Early intervention, including blood pressure management, is essential for preventing irreversible damage to vision. This report underscores the importance of an integrated multidisciplinary approach to managing aHUS, especially considering the systemic nature of the disease and its potential ocular implications.

Keywords: Hypertensive choroidopathy, papilledema, atypical hemolytic uremic syndrome, Siegrist streaks, Elschnig spots

INTRODUCTION

Hemolytic uremic syndrome (HUS) is a disorder characterized by a triad of hemolytic anemia, thrombocytopenia, and acute kidney injury, typically triggered by infections, particularly those caused by Shiga toxin-producing Escherichia coli. Atypical hemolytic uremic syndrome (aHUS) is an uncommon, genetically heterogeneous condition primarily caused by dysregulation of the alternative complement pathway. Unlike typical HUS, aHUS can result in multiorgan involvement, most commonly affecting the kidneys, leading to thrombotic microangiopathy and renal failure.[1]

While aHUS mainly affects the kidneys, ocular involvement in aHUS can present with significant retinal changes, and hypertensive choroidopathy is one of the less recognized manifestations. Ocular impairment is rare but if present, it can be a serious complication of aHUS. According to some case report studies, sudden onset symptoms easily lead to near or total loss of vision.[2-4] In spite of initiating the full treatment some patients still can have these symptoms and their visual deficits become permanent.[2,3,5] Hypertensive choroidopathy refers to retinal changes resulting from long-standing or poorly controlled hypertension that can lead to ischemic damage to the retinal and choroidal vasculature. These changes can manifest as Elschnig spots, Siegrist streaks, and papilledema, which are indicative of hypertensive retinopathy and reflect a systemic vascular compromise. While these ocular signs are well documented in systemic hypertension, their presence in aHUS is less frequently reported.

This case report presents a 20-year-old female diagnosed with aHUS at an early age who developed hypertensive choroidopathy as a result of long-standing hypertension associated with her underlying disease. The patient exhibited significant ocular findings, including bilateral papilledema, Elschnig spots, and Siegrist streaks, which were detected during routine ophthalmologic examination following an episode of intracranial hemorrhage. This case underscores the importance of early recognition of ocular manifestations in aHUS, as timely intervention can prevent irreversible visual impairment and aid in the management of systemic complications.

Given the systemic nature of aHUS and the potential for multiorgan damage, it is essential for clinicians to include ophthalmological evaluations as part of the multidisciplinary care approach. Regular monitoring of retinal health, along with the management of blood pressure and renal function, is critical in preserving both visual function and overall patient health.

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CASE

A 20-year-old female with a long-standing diagnosis of aHUS, first diagnosed at the age of 10 years, was referred to our hospital for further evaluation after presenting with an intracranial hemorrhage. Her medical history included recurrent episodes of hemolytic anemia, thrombocytopenia, and renal impairment, for which she had been under regular follow-up and treatment at an external center. Despite being on standard therapy for aHUS, including eculizumab, the patient had not received treatment for the past 2-3 years due of intermittent non-compliance and complications related to her underlying condition.

The patient presented to the nephrology unit following sudden onset of severe headache, syncope, and loss of consciousness. Blood pressure at the time of admission was found to be dangerously elevated at 270/120 mmHg, and a CT scan revealed an intraventricular hemorrhage, confirming the diagnosis of a hemorrhagic cerebrovascular accident (CVA). The patient had no prior history of hypertension or cardiovascular disease, which led to further investigation into the underlying cause of her condition.

During her hospitalization, the patient also reported bilateral visual disturbances and a gradual decrease in visual acuity, which prompted a referral to the ophthalmology department.

Upon presentation to the ophthalmology clinic, the visual acuity was 20/60 in the right eye (OD) and 20/50 in the left eye (OS).

Anterior Segment

The anterior segment examination result was unremarkable, with no signs of cataracts or anterior uveitis.

Fundus Findings

After pupillary dilation, a detailed fundus examination revealed significant retinal changes in both eyes.

Grade 2 papilledema and increased vascular tortuosity were observed in the OD. Elschnig spots and Siegrist streaks were also observed in the peripheral retina. The macula appeared intact, with no visible hemorrhage, exudate, or edema (Figure 1).

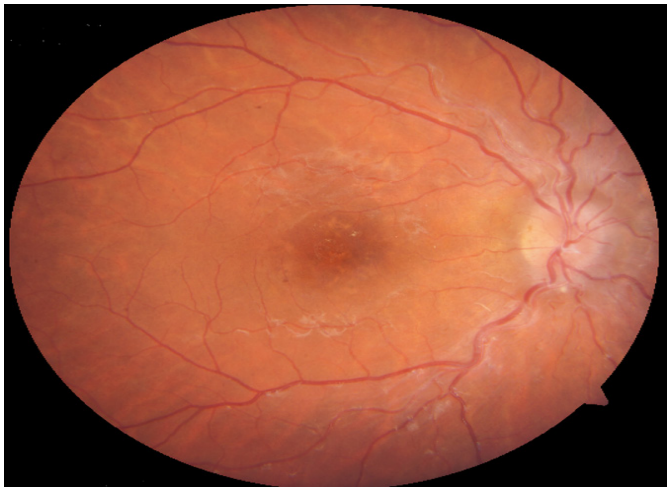

Figure 1. Colour fundus photograph of the right eye (OD)

Grade 3 papilledema was observed in the OS, with similar findings of Elschnig spots and Siegrist streaks in the peripheral retina. No significant macular edema or hemorrhage was observed (Figure 2).

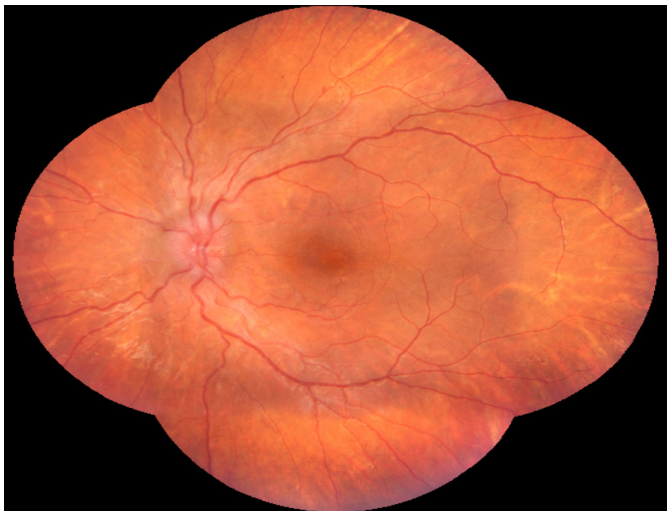

Figure 2. Colour fundus photograph of the left eye (OS)

Further diagnostic imaging was performed to evaluate the extent of retinal changes.

Fundus Autofluorescence (FAF)

FAF showed hypo-autofluorescence in the regions of Elschnig spots, indicating ischemic damage, and hyper-autofluorescence surrounding the ischemic areas due to hyperpigmentation (Figure 3).

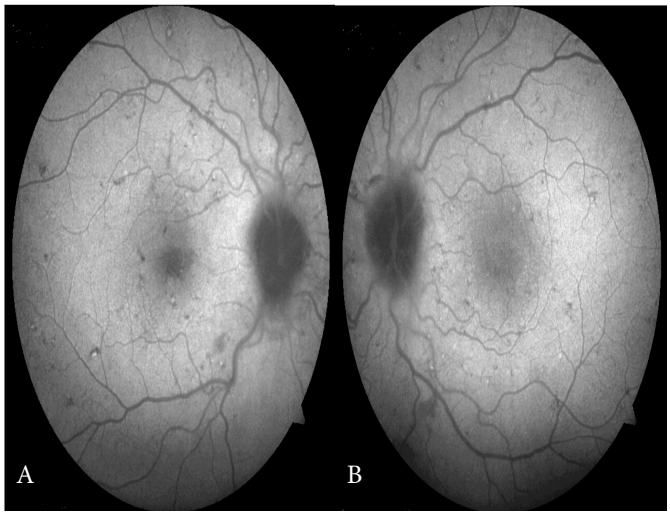

Figure 3. Fundus autofluorescence (FAF) image of the right and left eyes (OD and OS)

Fluorescein Angiography (FFA)

FFA revealed early patchy leakage and delayed choroidal filling at the sites of Elschnig spots. Siegrist streaks showed areas of hypofluorescence consistent with choroidal filling defects (Figure 4).

Optical Coherence Tomography (OCT)

OCT demonstrated elevation of the optical disc, consistent with papilledema. However, there was no evidence of retinal detachment or macular edema. The foveal contour remained preserved, which is a positive indicator of the patient's retained central vision (Figure 5).

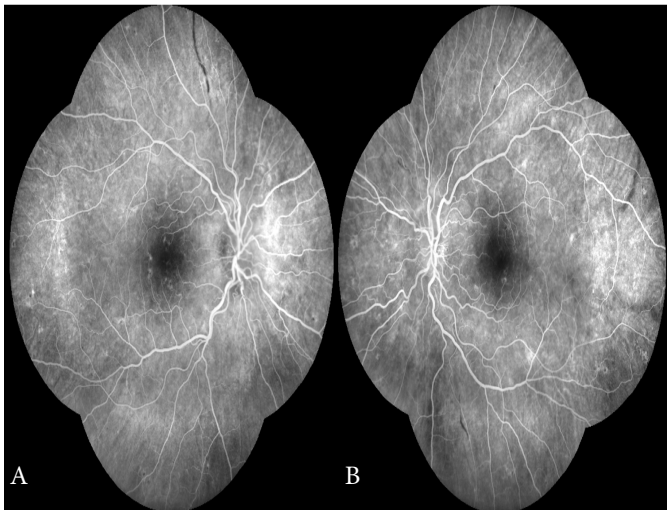

Figure 4. Fundus fluorescein angiography (FFA) of the right and left eyes (OD and OS)

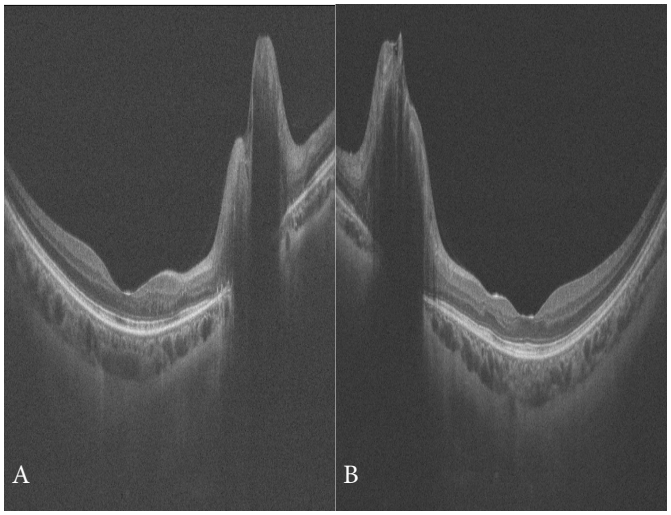

Figure 5. Optical coherence tomography (OCT) of the right and left eyes (OD and OS)

Upon confirming the diagnosis of hypertensive choroidopathy and papilledema associated with underlying aHUS, the patient was started on strict antihypertensive therapy to control her blood pressure, targeting a goal of <140/90 mmHg. Regular monitoring of renal function and continued treatment for aHUS were emphasized alongside scheduled follow-up visits with the ophthalmology department to track any changes in retinal findings.

The patient's condition was further managed in a multidisciplinary manner with nephrologists, ophthalmologists, and hematologists working together to optimize her care. Her blood pressure was gradually controlled, and follow-up fundus examinations showed no progression of retinal changes over the subsequent months. Regular ophthalmological examinations were scheduled to monitor the stability of her visual function and detect potential complications early.

At the time of her latest follow-up visit, the visual acuity remained stable at 20/60 in the OD and 20/50 in the OS. The papilledema had partially resolved, and the retinal findings of Elschnig spots and Siegrist streaks remained stable without any significant deterioration. Patients continue to be monitored for any systemic or ocular complications related to aHUS, with a strong emphasis on the importance of blood pressure control and regular retinal assessments.

DISCUSSION

aHUS is a rare genetically driven disorder primarily characterized by complement dysregulation, leading to systemic thrombotic microangiopathy. Although the renal manifestations of aHUS are well documented, the involvement of other organ systems, particularly the eyes, is less frequently reported. Ocular involvement in aHUS can range from subtle retinal changes to more severe conditions, such as hypertensive choroidopathy, which can lead to permanent vision loss if not diagnosed and managed early.

We present the case of a 20-year-old female with a longstanding diagnosis of aHUS who developed hypertensive choroidopathy in the context of poorly controlled hypertension. The patient exhibited Elschnig spots and Siegrist streaks, which are classic signs of hypertensive choroidopathy. These findings highlight the importance of regular ophthalmic evaluations in patients with aHUS, particularly those with long-term hypertension, as retinal findings can precede systemic complications and provide early indicators of disease progression.

Hypertensive choroidopathy, although commonly associated with systemic hypertension, is less frequently recognized in aHUS. Elschnig spots are small, round, pigmented areas of the retinal pigment epithelium that result from ischemia in the choriocapillaris, whereas Siegrist streaks are linear choroidal scars that reflect the chronicity of ischemic damage. In our case, both findings were observed in the periphery of the retina, indicating a significant vascular compromise. Papilledema, which was also noted in both eyes, is a direct result of elevated intracranial pressure, and can contribute to visual disturbances if left untreated.

FFA and FAF findings are crucial for confirming the ischemic nature of these retinal changes. The patchy leakage and delayed choroidal filling observed on FFA further supports the diagnosis of hypertensive choroidopathy. In addition, OCT allows for the visualization of papilledema without evidence of retinal detachment or macular edema, which is reassuring as it suggests the preservation of macular function and central vision.

Given the systemic nature of aHUS, this case highlights the need for an integrated approach to patient care involving not only nephrologists and hematologists, but also ophthalmologists. The early diagnosis of ocular changes can help prevent irreversible damage and preserve vision. Regular monitoring of blood pressure, renal function, and retinal health is essential in managing patients with aHUS, especially because they may not exhibit overt symptoms until significant complications arise.

Our case adds to the limited literature on the ocular manifestations of aHUS, particularly hypertensive choroidopathy. This underscores the importance of ophthalmic evaluation as part of the routine management of aHUS, especially in patients with long-term hypertension or those undergoing complement inhibitor therapy, as these patients are at an increased risk for vascular damage in multiple organ systems.

CONCLUSION

This case report illustrates the critical role of the early recognition and management of ocular manifestations in patients with aHUS. The presence of hypertensive choroidopathy in this patient, as evidenced by Elschnig spots and Siegrist streaks, highlights the need for routine ophthalmological assessment, particularly in patients with long-term hypertension. Timely intervention, including blood pressure control and regular monitoring of retinal health, is crucial to prevent irreversible visual impairment and manage the systemic complications of aHUS.

The findings of this case underscore the systemic nature of aHUS, emphasizing the importance of a multidisciplinary approach in managing these patients. Ophthalmologists, nephrologists, and hematologists must work together to ensure comprehensive care, allowing for the early detection of complications, improved patient outcomes, and preservation of both renal and visual functions.

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 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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Ankyra Medical Journal

Case Report

DOI: 10.51271/ANKMJ-0050

Rarely seen optic disc anomaly: a case of morning glory syndrome

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ABSTRACT

Morning glory syndrome (MGS) is a rare optic nerve anomaly, typically unilateral, characterized by a funnel-shaped macropapilla with neuroglial remnants at its center, surrounded by an elevated and pigmented chorioretinal ring. This condition may be associated with ocular and systemic abnormalities that can impair vision. A 14-year-old female presented to our clinic with a complaint of reduced vision in her right eye. Following a detailed ophthalmological examination and advanced imaging studies, the patient was diagnosed with morning glory disc anomaly (MGDA) in her right eye. This case highlights the importance of advanced imaging technologies in both the diagnosis and follow-up of MGS, as well as their role in the early detection of potential complications.

Keywords: Morning glory syndrome, optic disc, vision loss, ophthalmology

INTRODUCTION

Morning glory syndrome (MGS) is an uncommon anomaly of the optic disc that was first identified by Kindler in the 1970s. It derives its name from its visual similarity to the morning glory flower.[1] It is believed to arise from an anomaly in the development of the optic nerve during the embryonic stage. The syndrome is characterized by the enlargement of the optic disc, a central depression, and the presence of radially oriented blood vessels surrounding it.[2] MGS is typically regarded as a unilateral and congenital anomaly; however, there have been rare instances of bilateral cases documented in the literature.[3]

MGS is often regarded as a distinct anomaly; it may occasionally be linked to neurological disorders, craniofacial anomalies, or, in rare instances, genetic syndromes.[4] Complications related to MGS encompass retinal detachment and vitreoretinal traction, necessitating diligent observation.[5]

In this case report, we present a patient who visited our clinic reporting diminished vision in the right eye, subsequently diagnosed with MGS following a thorough examination. The clinical characteristics and diagnostic approaches related to the syndrome were analyzed in conjunction with existing literature.

CASE

A 14-year-old female presented to our clinic with recently noticed reduced vision in her right eye. The patient's medical history included asthma, with no history of trauma or similar eye conditions in her family. Visual acuity assessment using the Snellen chart showed uncorrected visual acuity of 4/10 and corrected acuity of 8/10 in the right eye, while the left eye was 10/10. Cycloplegic autorefraction revealed -0.50 spherical /-1.00 cylindrical axis 90 in the right eye and -0.25 spherical in the left eye. Anterior segment examination was unremarkable in both eyes. Direct and indirect light reflexes, as well as color vision, were normal. No relative afferent pupillary defect was observed.

Fundus examination revealed a large optic disc in the right eye with deep central excavation, radially arranged vascular structures, and findings characteristic of MGS (Figure 1). The left eye fundus was normal. Fundus autofluorescence (FAF) imaging revealed abnormal hyperfluorescent areas inferior to the right optic disc (Figure 2), with no pathological findings in the left eye. Optical coherence tomography (OCT) showed deep excavation of the right optic disc and surrounding retinal thinning (Figure 3). Humphrey visual field testing indicated an enlarged blind spot in the right eye (Figure 4).

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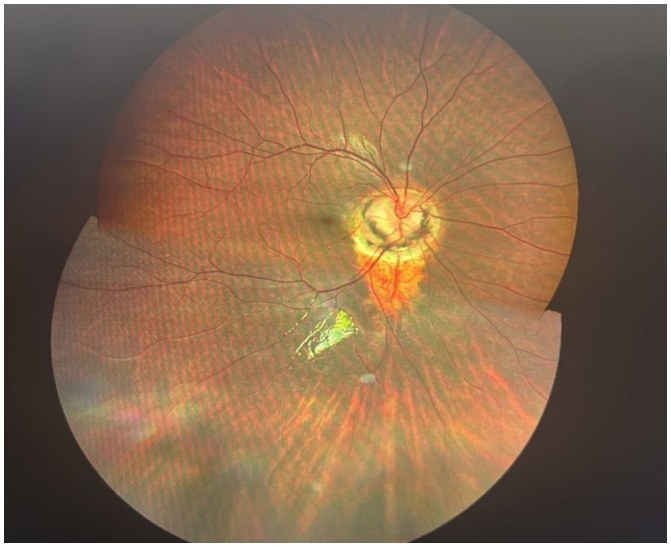

Figure 1. Fundus photograph of right eye

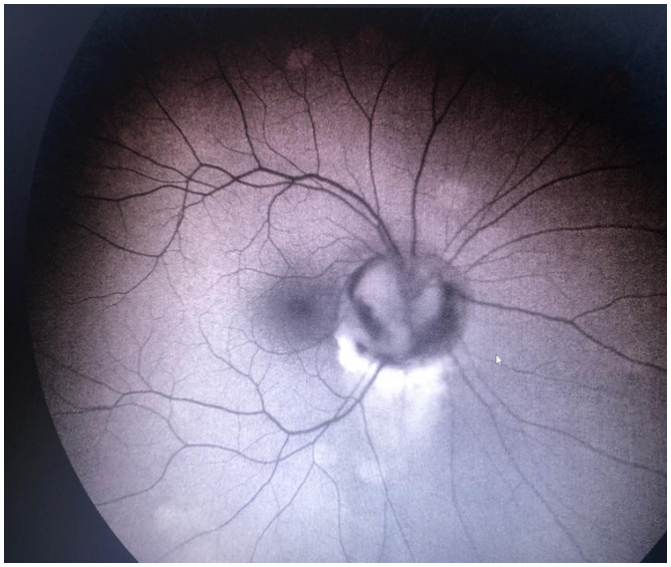

Figure 2. Fundus autofluorescence of right eye

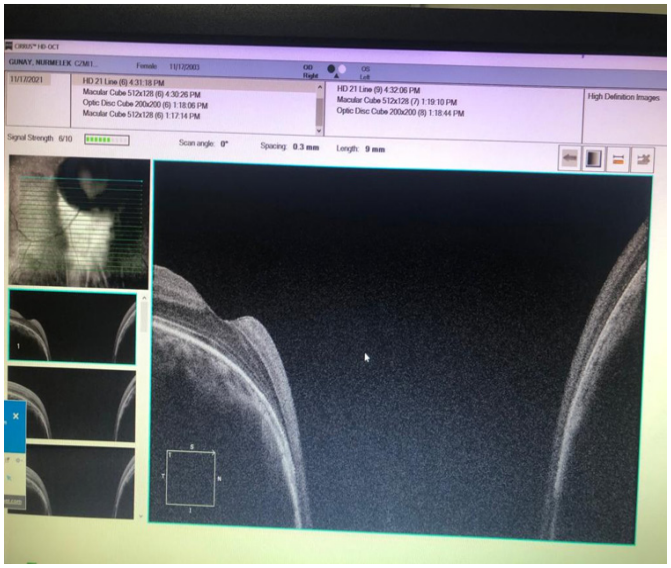

Figure 3. Optical coherence tomography of the patient's right eye

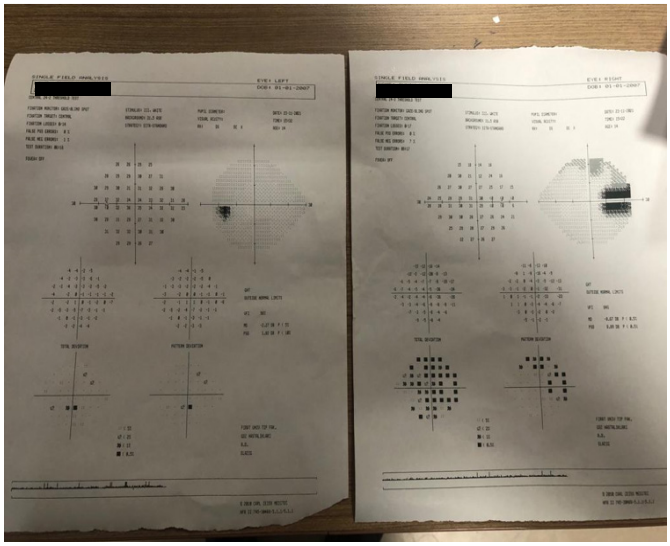

Figure 4. Visual field test photo of the patient

Systemic and neurological examinations revealed no abnormalities. Neurological imaging was not requested due to the absence of clinical findings.

The diagnosis of MGS was confirmed through fundus examination and advanced imaging findings. Given the patient's visual acuity loss in the right eye, the extent of anatomical anomalies was evaluated, and the risk of retinal detachment was carefully assessed. The patient and her family were informed about the irreversible nature of the condition and the importance of regular follow-ups.

In terms of treatment, there is no specific medical or surgical treatment for MGS. However, in this case, three basic approaches have been adopted:

1. Visual rehabilitation: The patient was prescribed glasses to help her adapt better, especially in her educational life.

2. Complication management: The patient was regularly followed up for the risk of retinal detachment. Accordingly, annual fundus examination and, if necessary, advanced imaging techniques were used to monitor retinal integrity.

3. Psychological support and awareness: Psychological counseling was recommended to the patient and his/her family to help them adapt to possible changes in their quality of life due to vision loss. In addition, information about MGS was provided to ensure that the patient and his/her family became aware of this rare condition.

Consent in writing was secured from the patient's family for the utilization results and images for scientific purposes.

DISCUSSION

MGS arises from the inadequate development of the optic disc during the embryonic stage. Recent research indicates that primary mesenchymal irregularities result in aplasia of the lamina cribrosa and insufficient closure of the posterior scleral wall, which play a role in the manifestation of MGS.[6] While often presenting as unilateral vision loss, MGS can

occasionally be associated with craniofacial anomalies or neurological disorders.[7] The optic disc appears enlarged, featuring a funnel-shaped depression at its center. This is associated with peripapillary chorioretinal pigmentary alterations that display orange or pink hues. Additionally, there is an increased presence of blood vessels compared to normal conditions. In contrast to the usual central branching pattern, these vessels demonstrate a radial curvature that resembles the petals of a flower as they radiate outward from the disc.[8]

Complications may arise, including serous retinal detachment, significant refractive errors, amblyopia, and strabismus, with instances of serous detachments documented in as many as 30% of cases.[9] The alterations in mechanical and hemodynamic factors at the periphery of the optic disc may increase the likelihood of choroidal neovascularization, potentially leading to subretinal edema and hemorrhage.[10] MGDA generally occurs infrequently, and no particular genetic mutation has been pinpointed in those affected. Nevertheless, research has revealed mutations in the PAX6 gene among eight patients exhibiting optic nerve anomalies, which includes one instance of bilateral MGDA.[11]

In the diagnosis of MGDA, morphological data provided by advanced imaging methods are as critical as clinical examination for differential diagnosis. OCT shows the funnel-shaped depression around the disc, the presence of subretinal fluid, and irregularities in the peripapillary retinal structure in detail, while fundus fluorescein angiography (FFA) helps detect vascular anomalies, areas of leakage, and possible choroidal neovascularization. Autofluorescence imaging supports the peripapillary morphology specific to MGDA by revealing retinal pigment epithelium (RPE) changes.

The most common differential diagnosis is optic disc coloboma. In coloboma, the depression is usually localized in the lower part of the optic disc, has regular borders, and is often observed bilaterally, whereas in MGDA, the depression is centrally located, and there are prominent peripapillary pigment changes around it and the vascular structure radiating from the disc (flower petal appearance) are the distinguishing features.[12] Therefore, when diagnosing MGDA, disc morphology, lesion location, accompanying retinal changes, and systemic/symptomatic findings should be taken into consideration; if necessary, differential diagnosis should be made with multimodal imaging and genetic tests. Making the differential diagnosis correctly is of vital importance, especially for the effective management of amblyopia and potential retinal complications.

In this case, the patient exhibited no systemic or neurological anomalies, and the syndrome was considered an isolated condition. Fundus imaging demonstrated the characteristic features of MGS, while OCT provided detailed insights into the disc's structural changes.

Accurate diagnosis of MGDA is essential for effective management, including distinguishing it from other congenital optic nerve disorders, such as typical optic nerve coloboma. Early treatment of amblyopia and potential complications is critical for preserving vision and improving outcomes.

CONCLUSION

MGS is a rare optic disc anomaly that requires careful attention in clinical practice. This case not only underscores the importance of early diagnosis and management strategies but also contributes to understanding this rare pathology. The details obtained through modern imaging techniques serve as a guide for both patients and clinicians. Utilizing advanced technologies in the diagnosis and follow-up of this condition is crucial for improving patient outcomes and preventing ophthalmological complications. This case aims to raise awareness of MGS and its potential challenges.

ETHICAL DECLARATIONS

Informed Consent

The parents of 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 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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