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Investigation of the prognostic value of blood parameters in patients with rinoserebral mucormycosis

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Abstract

Mucormycosis is a rapidly invasive, life-threatening opportunistic fungal infection, usually in immunocompromised patients. Suspicion, early diagnosis, debridement and anti-fungal treatment are important prognostic factors. The most common clinical manifestations of rhinocerebral mucormycosis are fever, headache, facial and ocular oedema. Invasion of surrounding tissues, the eye, skull base and brain is critical for disease progression. The purpose of this study was to investigate the predictive value of blood parameters in patients with mucormycosis. The preoperative 10-day blood parameters of 23 patients with clinical, radiological and pathological diagnoses of mucormycosis were compared in terms of etiology, gender and site of involvement. When the results were compared, the neutrophil-lymphocyte ratio (NLR) on days 1, 2, 5, 7, 8, 9, and 10 was significantly higher in patients with skull base involvement compared to those without skull base involvement ($p<0.05$). When comparing the regions of involvement, a significant correlation was found between cranial and turbinate involvement and between lamina papricea and ocular involvement ($p<0.05$). It was suggested that the NLR rate could be predicted as a poor prognostic factor in patients with mucormycosis.

Keywords: Mucor, NLR, Skull base involvement, blood parameters

Introduction

Mucormycosis is an opportunistic disease caused by a group of fungal pathogens called mucormycetes that is aggressive, rapidly progressive, and has a high mortality rate [1,2]. Mucormycetes spores are common in nature and can cause infection in immunosuppressed patients, usually by inhalation of fungal spores [3]. These inhaled spores can multiply in the nasal mucosa and spread by angio-invasion to adjacent structures, the orbita and the brain. The most commonly documented causes of mucormycosis are Rhizopus species, Mucor species and Lichtheimia species [1].

The most common risk factors in the aetiology of mucormycosis are chronic diseases such as diabetes mellitus, haemato-oncological diseases such as leukaemia, lymphoma, infectious diseases such as AIDS, tissue or stem cell transplantation, long-term steroid use, treatments such as chemotherapy and severe burns [5,6]. Despite this, there are cases reported in the literature of mucormycosis infection in the absense of risk factors [4].

Mucormycosis can be divided into six subtypes: rhinocerebral, pulmonary, cutaneous, gastrointestinal, disseminated and other [6]. The most common form is rhinocerebral mucormycosis [7]. Clinical manifestations of rhinocerebral mucormycosis include

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fever, headache, pain and oedema around the face and eyes, and nasal congestion. If the orbit is involved, proptosis and exotropia may be observed.

Although endoscopic examination, computed tomography (CT) and magnetic resonance imaging (MRI) play an important role in the diagnosis, the definitive diagnosis is made by histopathological examination. Mucoral hyphae 6-16 µm wide, but up to 25 µm, without or with a few septa are diagnostic. These hyphae form a ribbon-like appearance with an irregular branching pattern [1].

Suspected and confirmed cases of mucormycosis are considered emergencies and require immediate intervention, including surgical debridement with clear margins, administration of antifungal medication and review of the immunosuppressive situation. Depending on the severity of the infection, amphotericin B can be given at doses of 1 mg/kg to 10 mg/kg Daily [1]. Surgical treatment includes turbinectomy, palatal resection, resection of the lamina papyracea and extensive debridement, sometimes with orbital exenteration. Retrobulbar injection and/or sinus irrigation with amphotericin B may also be used [8].

In intense chronic inflammation such as mucormycosis, the high-stress environment increases the number of neutrophils and decreases the number of lymphocytes [9]. Previous studies have reported an increase in leukocytes and neutrophils and the incidence of lymphocytopenia in patients with mucormycosis [10,11]. However, a review of the literature indicates that data on complete blood counts in patients with rhinocerebral mucormycosis are minimal.

The neutrophil/lymphocyte ratio, which has been widely discussed in recent years and interpreted as an indirect indicator of the host's immune response capacity, is a possible indicator of the severity of mucormycosis, whether it affects orbital invasion and whether it can be treated. Data from early CBC can be used as a biomarker.

In this study, we desired to evaluate the prognostic significance of the last ten days' complete blood count values (CBC) (neutrophils, lymphocytes, white blood cells, platelets, haemoglobin, NLR) in patients diagnosed with rhinocerebral mucormycosis based on clinical, radiological and pathological findings.

Material and Methods

This study included 23 patients who were clinically, radiologically and pathologically diagnosed with rhinocerebral mucormycosis between January 2012 and April 2023 at Inonu University Department of Otolaryngology and Head and Neck Surgery. A total of 9 patients who did not have surgery, who did not have CBC values for the last 10 days, who had suboptimal radiological images, who had a history of previous orbital or sinonasal surgery, and who were histopathologically reported as "mucor suspicious" were excluded from the study. Participants' data were retrieved retrospectively from the hospital electronic database, files, radiology imaging system and pathology reports, and CBC parameters for the 10 days prior to debridement were assessed. Neutrophil, lymphocyte, leukocyte, platelet, haemoglobin and NLR values were recorded. The NLR was obtained by dividing the total neutrophil count by the total lymphocyte count. Patients' age, sex, nasal and paranasal sinus involvement, orbital invasion, skull base involvement, and aetiological factors were also analysed and compared. Before the study, approval was obtained from Inonu University Health Sciences Non-Interventional Clinical Research Ethics Committee on 15.11.2021 with decision number 2022/4113.

Statistical analysis

SPSS for Windows 20.0 (SPSS, INC, an IBM Company, Chicago, Illinois). Mann Whitney U test and Spearman's correlation rho efficient test were used. P-value <0.05 was considered statistically significant.

Results

In this study, there were 17 (73.9%) males and 6 (26.1%) females. The mean age of the patients was 48.69±22.27 years (ranging from 5.00 to 80.00 years).

Neutrophil count, lymphocyte count, WBC, platelet count, NLR and haemoglobin values of the patients (n=23) were shown in Table 1 and Figure 1.

Table 1. Neutrophil count, lymphocyte count, WBC, NLR and haemoglobin values of the patients (n=23)

		1st day	2nd day	3rd day	4th day	5th day	6th day	7th day	8th day	9th day	10th day
Neutrophil count	Mean	3.00	3.23	3.20	2.70	2.76	2.49	2.51	2.31	5.08	2.10
	Std.dev.	5.01	4.88	4.65	3.42	3.32	3.14	2.77	2.68	14.36	2.74
Lymphocyte count	Mean	1.75	1.32	1.23	0.96	1.01	0.66	0.72	0.66	0.69	0.68
	Std.dev.	2.39	2.22	2.37	1.57	1.67	0.76	0.73	0.72	0.95	0.96
NLR	Mean	9.44	12.93	11.54	9.16	8.89	8.01	8.23	8.63	12.49	12.15
	Std.dev.	25.07	27.24	24.69	15.78	17.51	13.05	14.69	21.48	39.72	38.88
WBC	Mean	6.24	5.59	20.16	4.15	3.96	4.44	4.86	4.00	4.36	4.72
	Std.dev.	12.09	8.48	71.99	4.61	4.63	5.51	7.22	6.07	6.86	7.81
Platelet count	Mean	80.76	82.84	88.13	89.17	83.86	86.30	82.13	76.08	77.08	72.21
	Std.dev.	109.75	111.83	115.37	109.59	101.45	99.37	102.60	96.28	102.55	89.48
Hemoglobin	Mean	9.96	10.14	10.18	9.89	9.76	9.65	9.56	9.40	9.31	12.20
	Std.dev.	1.26	1.207	1.72	1.24	1.45	1.43	1.52	1.22	1.21	14.60

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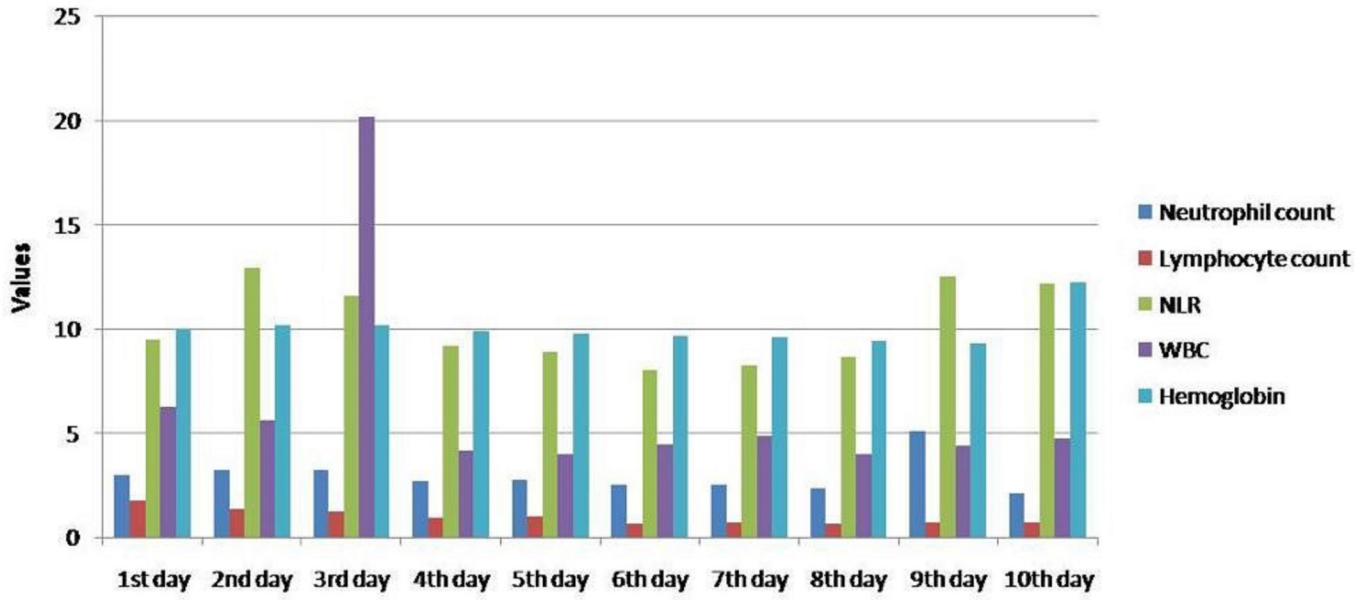

Figure 1. Neutrophil count, lymphocyte count, WBC, NLR and hemoglobin values of the patients (n=23)

Analysis according to the aetiology

Acute lymphoblastic leukaemia (ALL) aetiology was present in 8 patients (34.8%) and absent in 15 (65.2%). There were no significant differences between Lymphocyte and NLR values of the patients with or without ALL ($p>0.05$). In the ALL group, neutrophils (1st, 3rd days), WBC (1st to 6th days), PLT (4th and 6th days), and haemoglobin (9th days) values were significantly lower than those in the non-ALL group ($p<0.05$).

Acute myeloid leukaemia (AML) aetiology was present in 5 patients (21.7%) and absent in 18 (78.3%). There were no significant differences between neutrophil, WBC, platelet count, NLR and haemoglobin values of the patients with or without AML ($p>0.05$). On 3rd day, lymphocyte values of the AML group were significantly lower than that of the non-AML group ($p<0.05$).

Renal transplantation etiology was present in 3 (13.0%) and absent in 20 (87.0%). There were no significant differences between lymphocyte and haemoglobin values of the patients with or without renal transplantation ($p>0.05$). In the renal transplantation group, neutrophils (1-9th days), NLR (2-7th days), WBC (1-4th days) and PLT (3-5th days) values were significantly higher than those in the non-renal transplantation group ($p<0.05$).

Other aetiologies were present in 7 patients (30.4%). (multiple myeloma, burns, lung cancer, aplastic anaemia, myelodysplastic syndrome)

Analysis according to the gender

There were no significant differences between neutrophil, WBC, platelet count and haemoglobin values of the males and females ($p>0.05$). Lymphocyte values of the males were significantly lower than females on the 1st and 4th days ($p<0.05$). The NLR values of the males were significantly higher than that of females on the 1st, 8, 9 and 10th days ($p<0.05$).

Analysis according to the involvement regions

Skull base involvement

Skull base involvement was detected in 5 (21.7%) patients; 18 (78.3%) patients had no skull base involvement. There were no significant differences between the neutrophil, lymphocyte, WBC, platelet and haemoglobin counts of patients with and without skull base involvement ($p>0.05$). However, the NLR of skull base involvement was significantly higher than that of non-involved patients on days 1, 2, 5, 7, 8, 9 and 10 ($p<0.05$). On these days, the median NLR values were 11.23, 9.48, 7.31, 6.54, 4.91, 5.32 and 8.78 in patients with skull base involvement and 0.62, 0.83, 1.07, 2.03, 1.08, 1.25 and 0.65 in patients without skull base involvement.

Lamina papyracea involvement

Lamina papyracea involvement was found in 9 (39.1%) patients and there was no lamina papyracea involvement in 14 (60.9%) patients. There were no significant differences between neutrophil, lymphocyte, WBC, platelet count, NLR and haemoglobin levels in patients with and without lamina papyracea involvement ($p>0.05$).

Septum involvement

Septum involvement was detected in all patients (100.0%).

Turbinate involvement

Turbinate involvement was found in 9 (39.1%) patients and no turbinate involvement was found in 14 (60.9%) patients. There were no significant differences between neutrophil, lymphocyte,

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WBC, platelet count, NLR and haemoglobin values in patients with and without turbinate involvement (p>0.05).

Paranasal sinus involvement

Paranasal sinus involvement was found in 6 patients (26.1%) and there was no paranasal sinus involvement in 17 patients (73.9%). There were no significant differences between the neutrophil, lymphocyte, WBC, platelet and haemoglobin counts of the patients with and without paranasal sinus involvement (p>0.05). However, the NLR of patients with sinus involvement was significantly higher than that of patients without sinus involvement on day 6 (p<0.05). On day 6, the median NLR was 17.84 in patients with sinus involvement and 1.53 in patients without sinus involvement.

Spearman's correlation rho efficient test results were shown in Table 2.

There were positive correlations between skull base and turbinate involvement, lamina papyracea involvement and surgery for eye involvement (p<0.05) (Table 2).

There were positive correlations between skull base involvement and NLR values on days 1, 2, 5, 7, 8, 9 and 10 (p<0.05) (Table 2).

There were positive correlations between paranasal sinus involvement and 6-day NLR values (p<0.05) (Table 2).

In patients with turbinate involvement, haemoglobin values decreased on day 7 (p<0.05) (Table 2).

There were no significant correlations between age, gender, paranasal sinus and lamina papyracea involvement and skull base, lamina papyracea, turbinate and paranasal sinus involvement (p>0.05).

There were no significant correlations between the presence of ALL, AML, renal transplant and other aetiologies and skull base, lamina papyracea, turbinate and paranasal sinus involvement (p>0.05).

There were no significant correlations between neutrophil count, lymphocyte count, WBC count, platelet count and skull base, lamina papyracea, turbinate and sinus involvement (p>0.05).

Table 2. Spearman's correlation rho efficient test results

			Skull base involvement	Lamina papyracea involvement	Turbinate involvement	Paranasal sinus ninvolvement
Skull base involvement		**r**			0.423	
		p			0.045	
Turbinate involvement		**r**	0.423			
		p	0.045			
Operation for eye involvement		**r**		0.537		
		p		0.008		
NLR	**1st day**	**r**	0.604			
		p	0.002			
	2nd day	**r**	0.477			
		p	0.021			
	5th day	**r**	0.445			
		p	0.033			
	6th day	**r**				0.433
		p				0.039
	7th day	**r**	0.429			
		p	0.041			
	8th day	**r**	0.461			
		p	0.027			
	9th day	**r**	0.461			
		p	0.027			
	10th day	**r**	0.477			
		p	0.021			
Haemoglobin	**7th day**	**r**			-0.478	
		p			0.021	

Discussion

In this study, the preoperative 10-day blood values of 23 patients diagnosed with mucormycosis were examined and the NLR was found to be significantly higher on days 1, 2, 5, 7, 8, 9 and 10 in patients with skull base involvement compared to those without skull base involvement. When comparing the sites of involvement, a significant correlation was observed between skull and turbinate involvement and lamina papyracea and ocular involvement.

Rhinocerebral mucormycosis is an aggressive, opportunistic fungal disease that usually occurs in immunocompromised patients [11]. The most common site of mucormycosis is the

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middle turbinate, followed by the middle meatus and the septum. In undiagnosed or untreated cases, bone infiltration is expected. Involvement of the sphenopalatine and internal maxillary arteries in rhinocerebral mucormycosis leads to invasion of the brain and orbita. Involvement of the internal carotid artery and cavernous sinus thrombosis are common only in long-standing cases [12].

If the infection is restricted to the sinuses, the survival rate is 50-80%, but if the infection has progressed to the brain, the mortality rate is over 80% [13]. Survival rates of approximately 70% have been documented when amphotericin B is combined with early, aggressive surgery. Given the delay in diagnosis and treatment, most patients with mucormycosis have a poor prognosis [14].

Diabetes, one of the aetiologies of mucormycosis, impairs leukocyte phagocytosis, neutrophil chemotaxis and the local inflammatory response. In the mid-20th century, diabetes was considered an important risk factor for mucormycosis. In recent years, however, malignancy has become an important risk factor due to the increasing number of patients receiving chemotherapy or cancer immunotherapy [1]. The aetiological factors in our study support this statistic.

Data on complete blood count (CBC) in patients diagnosed with rhinocerebral mucormycosis are limited in the literatüre [10]. The incidence of neutrophilia and lymphocytopenia has been reported in patients with mucormycosis. Wahid et al. stated that NLR can be used as a possible indicator of the severity of COVID-related clinically staged rhinocerebral mucormycosis and as a prognostic factor in treatment. Mani et al [11] reported that angioinvasion and minimal neutrophilic inflammation are poor prognostic histopathological features in COVID-associated rhinoorbital mucormycosis. They reported that high NLR and diabetic ketoacidosis were associated with poor prognosis [15].

Our study investigated the prognostic value of NLR and other blood parameters in patients with rhinocerebral mucormycosis without COVID aetiology. We analysed the blood parameters of these patients 10 days before the diagnosis of rhinocerebral mucormycosis and investigated whether there was an effect on involvement and, if so, at what level.

Considering that the aetiological factors of the patients in the study may affect the blood parameters of the patients independently of mucormycosis, the aetiological factors were statistically evaluated by themselves and it was found that these factors did not cause a significant difference.

In our study, NLR was found to be statistically significantly higher in patients with skull base involvement than in patients without skull base involvement on days 1, 2, 5, 7, 8, 9 and 10 ($p<0.05$). These data support studies conducted in patients with COVID-related rhinocerebral mucormycosis [15]. However, there was no statistically significant correlation between NLR and other regional involvement.

On the other hand, the significant correlation between skull base and turbinate involvement in our study supports the theory that skull base and brain involvement is mediated by sphenopalatine and internal maxillary artery involvement [12]. As expected, a significant correlation was also found between the lamina papricea and orbital involvement ($p<0.05$).

Conclusion

In our study, the high NLR in patients with rhinocerebral mucormycosis with skull base involvement compared with patients without skull base involvement suggests that this ratio can be predicted as a poor prognostic value. Investigation and imaging for skull base involvement in cases with a high NLR may be recommended. Large case series are needed to make more definitive statements.

Limitation and recommendation

The limiting factor of our study was that other conditions that may affect the patients' blood parameters (medications, other infectious and systemic diseases) could not be standardised accurately. In a more extensive case series, it is recommended to compare blood parameters after treatment and to evaluate their prognostic and follow-up values.

Conflict of Interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical Approval
Approval was obtained from Inonu University Health Sciences Non-Interventional Clinical Research Ethics Committee on 15.11.2021 with decision number 2022/4113.

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