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ORIGINAL ARTICLE

Clinical and Neuroimaging Characteristics of Ischemic Stroke in Rhino-Orbito-Cerebral Mucormycosis Associated with COVID-19

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Abstract

Purpose The aim of this study was to compare clinical, neuroimaging, and laboratory features of rhino-orbito-cerebral mucormycosis (ROCM) in COVID-19 patients with and without ischemic stroke complications.

Methods This observational study was conducted between August and December 2021 and 48 patients who had confirmed ROCM due to COVID-19, according to neuroimaging and histopathology/mycology evidence were included. Brain, orbit and paranasal sinus imaging was performed in all included patients. Data pertaining to clinical, neuroimaging, and laboratory characteristics and risk factors were collected and compared between patients with and without ischemic stroke complications.

Results Of the patients 17 were diagnosed with ischemic stroke. Watershed infarction was the most common pattern ($N=13$, 76.4%). Prevalence of conventional risk factors of stroke showed no significant differences between groups (patients with stroke vs. without stroke). Cavernous sinus ($p=0.001$, odds ratio, OR = 12.8, 95% confidence interval, CI: 2.3–72) and ICA ($p<0.001$, OR = 16.31, 95%CI: 2.91–91.14) involvement was more common in patients with stroke. Internal carotid artery (ICA) size (on the affected side) in patients with ischemic stroke was significantly smaller than in patients without stroke (median = 2.4 mm, interquartile range, IQR: 1.3–4 vs. 3.8 mm, IQR: 3.2–4.3, $p=0.004$). Superior ophthalmic vein (SOV) size (on the affected side) in patients with stroke was significantly larger than patients without stroke (2.2 mm, IQR: 1.5–2.5 vs. 1.45 mm IQR: 1.1–1.8, $p=0.019$). Involvement of the ethmoid and frontal sinuses were higher in patients with stroke ($p=0.007$, OR = 1.85, 95% CI: 1.37–2.49 and $p=0.011$, OR = 5, 95% CI: 1.4–18.2, respectively). Patients with stroke had higher D-dimer levels, WBC counts, neutrophil/lymphocyte ratios, and BUN/Cr ratio (all $p<0.05$).

Conclusion Stroke-related ROCM was not associated with conventional ischemic stroke risk factors. Neuroimaging investigations including qualitative and quantitative parameters of cavernous sinus, ICA and SOV are useful to better understand the mechanism of stroke-related ROCM in COVID-19 patients.

Keywords COVID-19 associated mucormycosis · Mucormycosis associated stroke · Brain MRI · Cerebrovascular involvement · Internal carotid artery · Cavernous sinus

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Introduction

Mucormycosis, caused by fungi of the order Mucorales, can manifest as an angioinvasive fungal infection [1]. Some conditions such as overt diabetes mellitus, hematologic malignancies, and organ transplantation predispose patients to mucormycosis [2]. Different clinical presentations have been described, including pulmonary, cutaneous, gastrointestinal, rhinocerebral, and disseminated forms [3, 4]. An outbreak of mucormycosis has been described during the coronavirus disease 2019 (COVID-19) pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in India. There was a more than fivefold rise in hospital admissions due to invasive fungal infection during the COVID-19 pandemic compared to the previous 2 years [1, 5, 6].

There is no sufficient evidence on the exact incidence and risk factors for cerebrovascular events in mucormycosis patients. Two recent studies have reported that 11.8% and 14.8% of patients with COVID-19 associated mucormycosis (CAM) had cerebrovascular events, including different types of strokes [7–9]. Kulkarni et al. reported that ischemic stroke is the most common neurological manifestation [8]. Prior studies that assessed the imaging characteristics of rhino-orbito-cerebral mucormycosis (RCOM), had found paranasal sinus infection, orbital infection, arterial thrombosis, cavernous sinus thrombosis, cerebral hemorrhage, and mycotic aneurysms are among the findings in this group of patients [10].

Although some studies have reported on the clinical characteristics and epidemiology of neurological complications of CAM, there is a paucity of studies on the neuroimaging and laboratory findings in these patients. In this study, we aimed to compare clinical, neuroimaging, and laboratory features of ROCM in the setting of CAM between patients with and without ischemic stroke complications, to find the potential risk factors associated with stroke in these patients.

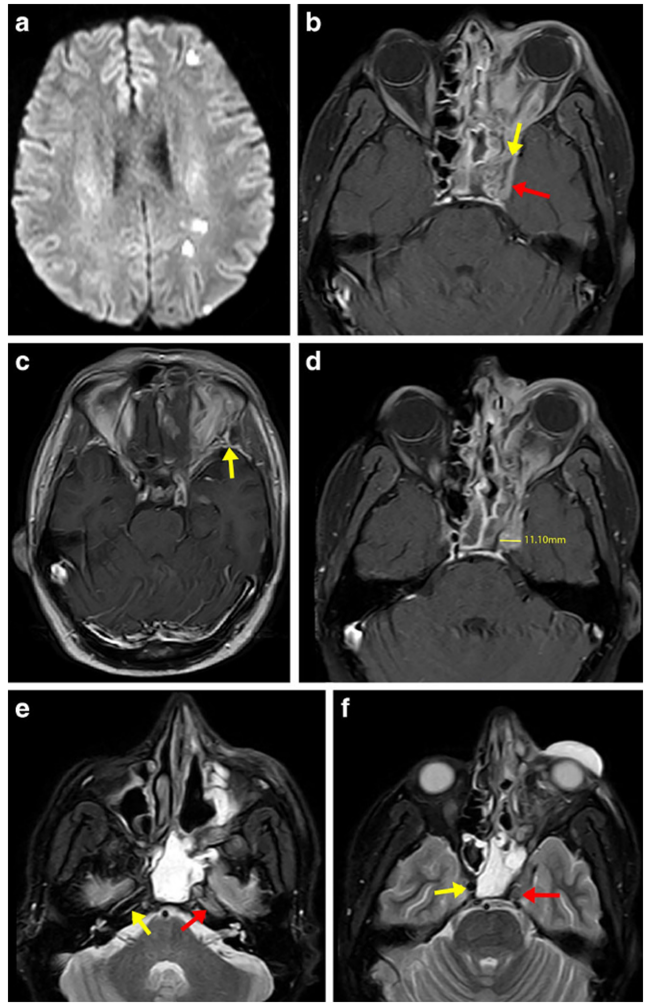

Fig. 1 A patient in his late 30s with history of COVID-19 infection three weeks before the admission for hypoesthesia in the left forehead and cheek for two days. It was accompanied by ptosis, proptosis, extraocular movement limitation, and diminished vision. Axial diffusion-weighted imaging (**a**) demonstrates unilateral ischemic stroke in deep (internal) and cortical (external) watershed zones. Axial postcontrast MRI showing a filling defect (*yellow arrow*) along with bulging of the lateral wall of the left cavernous sinus (*red arrow*) (**b**), dural enhancement in nearby left middle cranial fossa (*yellow arrow*) (**c**) and increased cavernous sinus width to 11.1 mm (*yellow arrow*) (**d**). Axial T2-weighted fat suppressed MRI showing increased signal intensity in petrosal (**e**) and proximal cavernous (**f**) segments of the left internal carotid artery (ICA) (*red arrows*). The normal right ICA is shown with *yellow arrows* (**e**,**f**)

Method

Study Design

This single-center, observational study included a total of 48 adult patients who were admitted to the largest medical center, exclusively designated for the care of COVID-19 patients in our country. They all had pertinent clinical and neuroimaging findings with histopathology/mycology confirmed ROCM due to CAM. The study period was between August 2021 and December 2021, during the fourth wave of COVID-19 outbreak in the country.

Subjects

A COVID-19 infection was diagnosed based on SARS-CoV-2 reverse transcription-polymerase chain reaction (RT-PCR) SARS-CoV-2 viral ribonucleic acid (RNA) or positive rapid antigen test (Arvin Biohealth Co., Tehran, Iran) on oropharyngeal and nasopharyngeal swab specimens. The initial diagnosis of mucormycosis was made by clinical and imaging evaluations of patients who presented with suspicious symptoms including new onset ptosis,

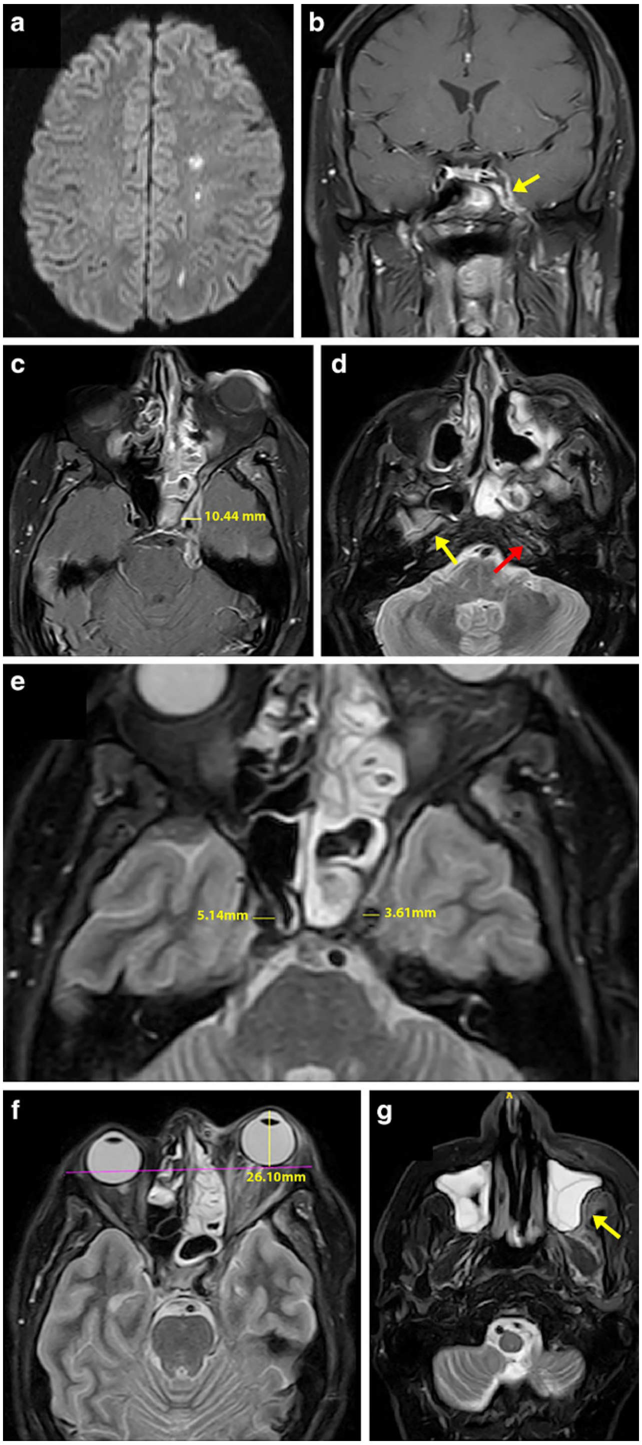

Fig. 2 A patient in his early 30s with history of COVID-19 infection four weeks before the admission for hypoesthesia of the left forehead and cheek for two days. It was accompanied by ptosis, proptosis, frozen eyes, and diminution of vision. Histological evaluation confirmed the diagnosis rhino-orbito-cerebral mycosis. Axial diffusion-weighted imaging (**a**) demonstrates unilateral watershed zone ischemic stroke. Post-contrast brain MRI shows a filling defect and bulging of the lateral wall of the left cavernous sinus (*yellow arrow*) (**b**) with the cavernous sinus width increased to 10.4 mm (**c**). Axial fat suppressed T2-weighted MRI shows subtle increased signal intensity in and around the petrosal segment of the left internal carotid artery (ICA) (*red arrow*) with the unaffected right ICA shown with a *yellow arrow* (**d**). ICA dimeters in the affected (3.6 mm) and non-affected (5.1 mm) sides are shown (**e**). Axial fat suppressed T2-weighted MRI showing proptosis of left eye (26 mm protrusion, anterior to the interzygomatic line at the level of the lens) (**f**) and abnormal signal affecting the periantral (perimaxillary) fat on the affected side (*yellow arrow*) (**g**)

facial numbness, extraocular movement restriction, and diminution of vision. The initial diagnosis was confirmed based on histopathology and mycology evaluation of biopsied tissues including staining with potassium hydroxide (KOH) or calcofluor stain of obtained tissue and/or fungal growth in cultures. CAM was defined based on previous literature as mucormycosis occurrence in patients with confirmed COVID-19 diagnosis within the prior 12 weeks [11]. ROCM was defined as histopathology confirmed mucormycosis infection in the samples from nose, paranasal sinuses, orbit, and/or intracranial structures.

All patients underwent brain computed tomography (CT) with or without magnetic resonance imaging (MRI) of the brain, orbits, and paranasal sinuses. The MRI protocol in patients with possible diagnosis of ROCM included T1 weighted image (T1WI), T2WI, fluid attenuation inversion recovery (FLAIR), T2WI with fat suppression, gradient recalled echo (GRE), diffusion-weighted imaging (DWI) with apparent diffusion coefficient (ADC), magnetic resonance angiography, magnetic resonance venography, and postcontrast T1WI sequences, except in cases with MR contraindications. All neuroimaging studies were evaluated by a radiologist (S.H. with more than 10 years of experience) and one neurologist (M.S. with more than 20 years of experience and neuroradiology fellowship). In order to determine the potential risk factors associated with stroke in CAM patients, cases were divided into two groups based on whether they had schemic stroke or not. The etiology of ischemic stroke was further established utilizing additional vascular imaging modalities (e.g., cervical and transcranial color Doppler ultrasound, CT angiography, MR angiography), cardiac evaluations (including echocardiography and electrocardiogram).

Variables

Demographic and clinical historical data were acquired from the patients directly or the patients' relatives upon enrolment. We collected conventional medical risk factors for stroke including hypertension (HTN), diabetes mellitus (DM), ischemic heart disease (IHD), hyperlipidemia (HLP), heart failure (HF) and atrial fibrillation (AF). We also recorded the detailed neurological examination data at the time of admission, the time interval between diagnosis of COVID-19 and mucormycosis, and patient survival outcome.

Imaging features including pattern of stroke (watershed/non-watershed), laterality, and vascular territory as well as imaging features related to of the cavernous sinus, internal carotid artery (ICA), superior ophthalmic vein (SOV), cerebral parenchyma, paranasal sinuses, soft tissue spaces surrounding the paranasal sinuses, and orbits were evaluated for all patients. Cavernous sinus involvement was considered positive as lateral wall bulging (Fig. 1b and 2b), increased signal intensity on spin echo MRI, postcontrast filling defect (Fig. 1b), associated dural enhancement (Fig. 1c), and asymmetric increase in cavernous sinus size measurement (Fig. 1d and 2c). Cavernous sinus size was measured as maximum width of cavernous sinus on the axial plane (Fig. 1d and 2c). ICA involvement was considered as asymmetrically increased signal intensity in the ICA and its adventitia (Fig. 1e,f and 2d), and asymmetric decrease in size of ICA lumen (Fig. 1f and 2e). ICA size was calculated based on the flow void diameter of the vertical C3/C4 segments of the ICA perpendicular to the axial plane just as it enters the cavernous sinus (Fig. 2e). SOV involvement was delineated by asymmetric increase in size of SOV lumen, increased signal intensity in the SOV, and enhancement of adventitia of SOV. SOV diameter was measured perpendicular to the SOV on coronal images on the closest slice to the rear of the globe. Proptosis was defined as a globe protrusion of more than 21 mm anterior to the interzygomatic line at the level of the lens on axial images (Fig. 2f; [12]). Ischemic stroke subtypes were categorized according to TOAST criteria classification: 1) large artery atherosclerosis, 2) cardioembolism, 3) small vessel occlusion, 4) stroke of other determined etiology, and 5) stroke of undetermined etiology [13].

Statistical Analysis

Statistical analysis was conducted using IBM SPSS Statistics for Windows, Version 26.0 (Armonk, NY, USA). Quantitative results are presented as median (interquartile range). Categorical variables were reported as counts and percentages, as appropriate, χ^2-tests were used to compare categorical variables and odds ratios (OR, 95% confidence interval, CI) were calculated for dichotomous variables. Mann-Whitney U test and Wilcoxon signed-rank test were applied to compare continuous variables between two groups and two related samples, respectively. A P value < 0.05 was considered as the level of statistical significance.

Results

Demographics and Clinical Characteristics

Over the study period, 75 patients were admitted to our hospital with the clinical suspicion of ROCM and recent history of COVID-19 and 59 patients had neuroimaging findings suggestive of possible ROCM; however, histopathology confirmed the diagnosis in only 50 patients. Of the patients two were excluded due to the history of COVID-19 preceding the 12-week period before clinical onset of ROCM (Fig. 3) and 48 patients (34 males, and 14 females) were included in the analysis with a median age of 58.5 years (IQR: 46–65.5 years) (Table 1). Of the 48 patients, acute ischemic stroke (AIS) was diagnosed in 17 (35.4%). The median interval time between the first symptoms of COVID-19 and first symptoms of ROCM was 15 days (IQR: 9.75–23.2 days) and there was no statistically significant difference between patients with and without AIS (15 days, IQR: 5–25 days vs. 15 days, IQR: 12.5–22.5, $P = 0.472$). Prevalence of conventional risk factors of stroke, i.e. HTN, DM, IHD, HLP and AF, showed no statistically significant differences between the two groups. Neurological examination of patients at the time of admission also showed no significant differences in terms of cavernous sinus related symptoms; however, other symptoms including hemiparesis, hemi-hypoesthesia and dysarthria were more common among patients with ischemic stroke (all $p < 0.05$).

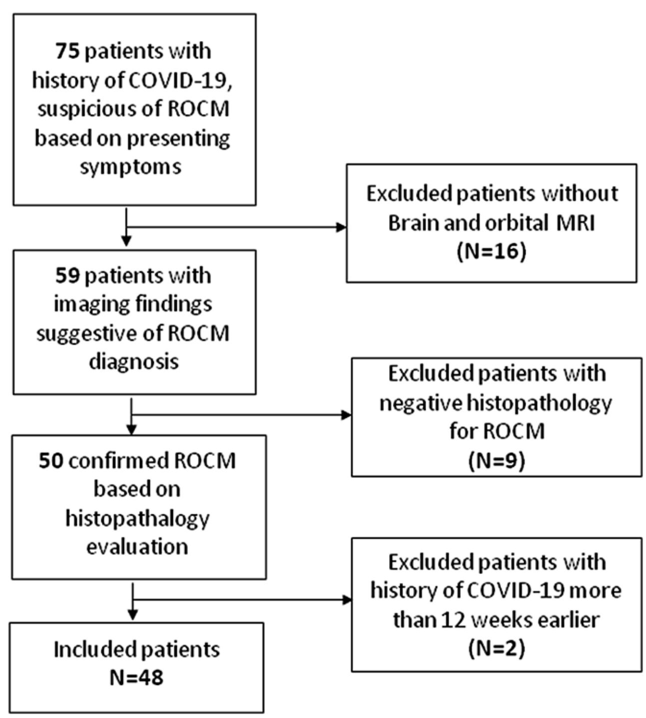

Fig. 3 The study workflow diagram for the selection of patients with rhino-orbito-cerebral mucormycosis (RCOM)

Table 1 Demographics, risk factors, and neurological examination at the time of admission

		Total ($n = 48$)	AIS ($n = 17$)	Without AIS ($n = 31$)	p Value	OR (95% CI)
Age (years)[a]		58.5 (46–65.5)	56 (41.5–65)	59 (49–66)	0.353	n/a
Gender	Male	34	13	21	0.525	1.5 (0.4–5.9)
	Female	14	4	10		
Conventional stroke risk factors	HTN	18	6	12	0.75	0.8 (0.2–2.8)
	DM	32	9	23	0.135	0.39 (0.11–1.4)
	IHD	9	2	7	0.359	0.45 (0.08–2.5)
	HLP	5	1	4	0.426	0.4 (0.04–3.97)
	AF	1	1	0	0.174	n/a
Duration between mucormycosis and COVID-19 diagnoses (days)[a]		15 (9.75–23.2)	15 (5–25)	15 (12.5–22.5)	0.472	n/a
Neurological examination in admit	Ptosis	26	11	15	0.278	1.95 (0.58–6.61)
	Facial numbness	20	5	15	0.202	0.44 (0.12–1.56)
	Extra ocular movement restriction	29	12	17	0.286	1.97 (0.56–6.98)
	Diminution of vision	33	14	19	0.132	2.94 (0.7–12.45)
	Impaired pupillary reflex	28	12	16	0.202	2.25 (0.64–7.92)
	Limb weakness	6	5	1	0.009*	12.5 (1.3–118.4)
	Limb hypoesthesia	4	4	0	0.005*	3.38 (2.14–5.34)
	Dysarthria	6	5	1	0.009*	12.5 (1.3–118.4)
	Headache	38	15	23	0.252	2.61 (0.48–14)
Death in hospital		10	7	3	0.001*	6.53 (1.4–30.2)

HTN hypertension, *DM* diabetes mellitus, *IHD* ischemic heart disease, *HLP* hyperlipidemia, *AF* atrial fibrillation, *n/a* not applicable, *OR* odds ratio, *CI* 95% confidence interval, *AIS* acute ischemic stroke

*p value < 0.05

[a]Quantitative data reported as Median (interquartile range)

Ten patients died during hospitalization, which includes 41.1% ($N = 7$) of patients with ischemic stroke and 9.6% ($N = 3$) of patients without ischemic stroke (OR = 6.53, 95% CI: 1.4–30.2, $P = 0.001$) (Table 1).

Neuroimaging Findings

All included patients underwent MRI, 17 patients had ischemic stroke and 5 patients had intraparenchymal abscesses, including in the cerebellum ($N = 2$), temporal lobe ($N = 2$), and frontal lobe ($N = 1$). The cavernous sinus was involved in 10 patients (20.8%), 8 of those developed AIS and 2 did not have any infarcts (OR = 12.8, 95% CI: 2.3–72, $p = 0.001$). There were no differences between patients with and without stroke in terms of bulging of cavernous sinus lateral wall, cavernous signal intensity in spin echo sequence (flow void vs. increased signal intensity), cavernous sinus filling defect, and dural enhancement. There were also no differences between patients with and without ischemic stroke with respect to the width of the cavernous sinus (Table 2).

The ICA was involved in 11 patients (22.9%), 9 of those patients developed ischemic stroke (OR = 16.31, 95% CI: 2.91–91.14, $p < 0.001$). ICA signal intensity on spin echo sequence showed preservation of the ICA flow void on the affected side in 3 patients and increased signal intensity in 8 patients (all in those patients with ischemic stroke) ($p = 0.011$). ICA diameter (on the affected side) in patients with ischemic stroke was significantly smaller than patients without stroke (2.4 mm, IQR: 1.3–4 vs. 3.8 mm, IQR: 3.2–4.3, $p = 0.004$) (Table 2). SOV was involved in 8 patients (16.6%), 5 patients had ischemic stroke and 3 did not ($p = 0.079$). SOV signal intensity in spin echo sequence showed flow void on the affected side in 2 patients (both in patients without ischemic stroke) and increased signal intensity in 6 patients (5 had ischemic stroke and 1 in the other group) ($p = 0.035$). SOV size (on the affected side) in patients with ischemic stroke was significantly larger than patients without ischemic stroke (2.2, IQR: 1.5–2.5 vs. 1.45, IQR: 1.1–1.8, $p = 0.019$) (Table 2).

Imaging of the paranasal sinuses revealed maxillary sinus, ethmoid sinus, sphenoid sinus, and frontal sinus involvement in 43 (89.5%), 37 (77%), 34 (70%) and 22 (45%) patients, respectively. Involvement of ethmoid (OR = 1.85, 95% CI: 1.37–2.49, $p = 0.007$) and frontal (OR = 5, 95% CI: 1.4–18.2, $p = 0.011$) sinuses were significantly higher

Table 2 Imaging findings of rhino-orbito-cerebral mucormycosis (ROCM)

	Total ($N=48$)	AIS ($N=17$)	Without AIS ($N=31$)	p Value	OR (95% CI)
Cavernous sinus features					
A. Cavernous sinus involvement	10	8	2	0.001*	12.8 (2.3–72)
A.1. Cavernous sinus lateral wall bulging	3	2	1	0.490	0.33 (0.01–8.1)
A.2. Cavernous signal intensity on spin echo MRI				0.301	n/a
Flow void	3	3	0		
Increased signal intensity	7	5	2		
A.3. Cavernous sinus filling defect	2	2	0	0.429	0.75 (0.5–1.1)
A.4. Nearby abnormal dural enhancement	6	4	2	0.197	1.5 (0.8–2.6)
B. Cavernous sinus size (mm)[a]	6.6 (6.1–8.3)	6.4 (5.3–7.3)	6.8 (6.3–8.6)	0.178	n/a
ICA features					
A. ICA involvement	11	9	2	0.001*	16.3 (2.9–91.1)
A.1. ICA signal intensity on spin echo MRI				0.011 *	n/a
Flow void	3	1	2		
Increased signal intensity	8	8	0		
A.2. ICA enhancement	4	3	1	0.809	1.5 (0.05–40.6)
B. ICA size (mm)[a]	3.6 (2.5–4.2)	2.4 (1.3–4)	3.8 (3.2–4.3)	0.004	n/a
Superior ophthalmic vein features					
A. SOV involvement	8	5	3	0.079	3.9 (0.8–19)
A.1. SOV signal intensity in spin echo MRI				0.035	n/a
Flow void	2	0	2		
Increased signal intensity	6	5	1		
A.2. SOV enhancement	5	3	2	0.439	n/a
B. SOV size (mm)[a]	1.6 (1.2–2.1)	2.2 (1.5–2.5)	1.45 (1.1–1.8)	0.019	n/a
Intraorbital involvement	27	13	14	0.079	3.25 (0.8–12.4)
Proptosis	16	7	9	0.43	1.6 (0.47–5.6)
Paranasal sinus involvement					
Maxillary	43	15	28	0.821	0.8 (0.1–5.3)
Frontal	22	12	10	0.011	5 (1.4–18.2)
Sphenoid	34	15	19	0.049	4.7 (0.91–24.5)
Ethmoid	37	17	20	0.007*	1.85 (1.37–2.49)
Nasal cavity	35	14	21	0.351	2 (0.46–8.7)
Periantral (perimaxillary) fat signal abnormality	36	10	26	0.03*	0.22 (0.05–0.91)
Superior orbital fissure involvement	9	5	4	0.329	2.1 (0.46–9.8)

AIS acute ischemic stroke, *OR* odds ratio, *CI* 95% confidence interval, *n/a* not applicable, *ICA* Internal carotid artery, *SOV* Superior ophthalmic vein

[a]Quantitative data reported as Median (interquartile range), p value

in patients with stroke ($p=0.009$ and 0.041, respectively). Involvement of other sinuses showed no significant differences between patients with stroke and without stroke. Involvement of superior orbital fissure showed no significant differences between patients with and without stroke ($p=0.329$). Presence of periantral fat signal abnormalities was significantly higher in patients without stroke (OR = 0.022, 95% CI: 0.05–0.91, $p=0.03$) (Table 2).

Stroke Characteristics

Using the TOAST classification of stroke, among the patients with AIS, most were categorized as other determined etiology ($N=13$, 76.4%) and 5 patients (29.4%) were classified as undetermined etiology (negative results after standard evaluation). Regarding the laterality of AIS, 13 patients (76.4%) had unilateral cerebral hemisphere stroke and 4 patients (23.5%) had bilateral stroke. In terms of the affected territory, anterior circulation was involved in 2 patients (11.7%) (2 anterior cerebral artery territory), pos-

Table 3 Baseline laboratory findings of patients at the time of hospital admission

Biomarker[a]	Total (*n* = 48)	AIS (*n* = 17)	Without AIS (*n* = 31)	*p* Value
Erythrocyte sedimentation rate, mm/hour	56 (35–80)	74 (49–85.5)	53 (28.5–72.5)	0.82
C-reactive protein, mg/L	62.5 (4.5–80.75)	78 (50–84)	13 (2–80)	0.148
D-Dimer, ng/mL	1350 (520–2500)	2100 (1200–3100)	850 (510–2074)	0.031*
White blood cell count, /mm3	11,800 (8400–15,700)	15,100 (10,900–16,875)	11,100 (7900–14,900)	0.023*
Lymphocyte percentage	11 (7.4–21.2)	8.45 (6.25–11.2)	16.8 (8.8–27.2)	0.01*
Neutrophil to lymphocyte ratio	7.54 (3.43–11.7)	10.1 (7.4–14)	4.6 (2.5–9.7)	0.01*
Hemoglobin, g/dl	12.1 (10.9–13.2)	12.7 (11.1–13.2)	11.8 (10.9–13.5)	0.87
Platelet count, /mm^3	258×10^3 ($176\times10^3-329\times10^3$)	253.5×10^3 ($186.7\times10^3-314\times10^3$)	263×10^3 ($167\times10^3-358\times10^3$)	0.472
Alanine aminotransferase, U/L	32 (21–47)	32 (21.7–39)	28.5 (18.2–53.7)	0.88
Aspartate aminotransferase, U/L	24 (16–33)	21.5 (15.2–27.2)	27 (18.5–35.2)	0.2
Blood urea nitrogen (BUN), mg/dl	17 (12–26)	22.5 (15.2–27)	15 (11–24)	0.074
Creatinine (Cr), mg/dl	1 (0.9–1.15)	1 (0.8–1.1)	1 (0.9–1.2)	0.49
BUN/Cr ratio	16 (11.5–22.1)	21.4 (15.8–23)	14.7 (10.9–19.1)	0.048*
Blood glucose, mg/dl	228 (150–313)	243 (185–371)	203 (126.5–279)	0.16

AIS Arterial Ischemic Stroke

*p value < 0.05

[a]Quantitative data reported as Median (interquartile range)

terior circulation was involved in 2 patients (10.5%), and 13 patients (76.4%) had watershed (border zone) infarcts. Of those with a watershed infarct pattern, the involvement was that of deep (internal) watershed in 8 patients, cortical (external) watershed in 1 patient, and mixed internal and external watershed infarcts in 4 patients.

Laboratory Data

Patients with AIS had a higher D-dimer level (2100 ng/mL, IQR: 1200–3100 vs. 850 ng/mL, IQR: 510–2074], $p = 0.031$), white blood cell count (15,100 per µL, IQR: 10,900–16,875 vs. 11,100 per µL, IQR: 7900–14,900, $p = 0.023$), and neutrophil to lymphocyte ratio (NLR) (10.1, IQR: 7.4–14 vs. 4.6, IQR: 2.5–9.7, $p = 0.01$). Lymphocyte percentage was significantly lower in patients with AIS (8.45%, IQR: 6.25–11.2 vs. 16.8%, IQR: 8.8–27.2, $p = 0.01$). Moreover, BUN/Cr ratios were significantly higher in patients with AIS (21.4, IQR: 15.8–23 vs. 14.7, IQR: 10.9–19.1, $p = 0.048$). Other laboratory values showed no significant differences between patients with and without ischemic stroke (Table 3).

Discussion

Rhino-orbito-cerebral mucormycosis (RCOM) is a life-threatening condition which needs timely attention to prevent severe complications. These infections are often difficult to diagnose. Knowledge of the clinical, neuroimaging, and laboratory features of ROCM in patients with CAM and the possible risk factors associated with stroke in these patients can be helpful for better management of these patients.

Lack of significant differences in conventional risk factors of ischemic stroke between patients with/without ischemic stroke suggests that the core mechanism of stroke in ROCM is different from stroke in other typical settings. Stroke in ROCM can be caused by invasion of vessels, local spread to nearby arteries, and hematogenous spread [14]. ROCM is an invasive disease with predilection for the vessels which pass through the nasal mucosa and paranasal sinuses. It can reach the cavernous sinuses either directly via the walls of the sphenoid sinus or via the pterygopalatine fossa [15]. Mucormycosis extension into the cavernous sinus with resultant septic thrombophlebitis and subsequent reactive vasospastic narrowing or frank invasion of ICA may result in occlusion or significant narrowing of the ICA, which in turn can cause ischemic stroke [6, 14]. Involvement of the basilar artery by further fungal invasion of the skull base may cause stroke in the posterior circulation [16].

Watershed infarct was the most common pattern of ischemic stroke among our patients (73%). Watershed infarction can be defined as the lack of blood supply in junctional areas between vascular territories of the major cerebral arteries and is most commonly seen in patients with significant arterial stenosis or prolonged severe hypotension. In our study, among 17 patients with AIS, 9 of 17 had ICA involvement and watershed infarct was the pattern of AIS in all of these 9 patients. In other patients without evidence of ICA involvement, half of them also had watershed infarct. These findings suggest that structural narrowing of carotid from the outside is not the only mechanism for stroke in RCOM patients and other mechanisms of AIS such as microscopic invasion of ICA could be considered in ROCM patients as well [9].

To best of our knowledge, there is no study that details the structural qualitative and quantitative imaging characteristics of cavernous sinus, ICA, SOV, paranasal sinuses and orbit in patients with AIS in the setting of ROCM associated with COVID-19. Although cavernous sinus involvement is more common among patients with AIS, other imaging features including size of cavernous sinus showed no significant differences between patients with and without AIS. These findings suggested that the key factor for ischemic stroke is the effect of cavernous sinus involvement on the ICA and that the mere size or pattern of cavernous sinus involvement may not have the determining role in ischemic stroke.

Among the various venous connections of the cavernous sinus, the superior and inferior ophthalmic veins are important afferent tributaries that drain into the cavernous sinus.

Presence of cavernous sinus thrombosis can impair the drainage of blood from the SOV, leading to engorgement or thrombosis of the SOV, thus it can be considered as an indirect sign of cavernous sinus involvement [12]. In line with this fact, our study showed that diameter of SOV in patients with stroke is larger than patients without stroke. Also, increased signal intensity of SOV on spin echo MRI sequence was more prevalent in patients with stroke. This finding can be due to blood stasis and possible thrombosis in SOV that may be sign of more extensive involvement of cavernous sinus that result in stroke [12, 17].

The cavernous segment of the ICA is an important component that can be significantly affected in the presence of cavernous sinus lesions. Involvement of ICA could be due to external compression (secondary to cavernous sinus involvement), intraluminal obstruction, and angioinvasion of fungus [12]. In our study, radiological evidence of ICA involvement showed significant differences regarding ICA lumen diameter between patients with and without stroke. Accordingly, comparing ICA diameter of involved side vs. uninvolved side in each group revealed a significant difference only in patients with stroke, which signify the importance of ICA evaluation in these patients. An arterial clot can alter signal intensity that would be different from the normal dark flow void (because of fast flowing blood) [18]. Thus, increased signal intensity of ICA on spin echo MRI (lack of flow void) can be indicative of slow flow or an ICA occlusion [18]. Similarly, our results showed that increased signal intensity of ICA on MRI is more common among patients with AIS. Regarding paranasal sinus involvement, our study showed that the ethmoid and frontal sinuses are the most commonly affected sinuses, which is in accordance with the study of Dubey et al. [9]. In addition, we presume that the higher involvement of frontal and ethmoid sinuses among stroke patients could be because of more extensive fungal spread or the proximity of the ethmoid sinus to ICA [19].

A hyperinflammatory state from cytokine storm followed by a prothrombotic state can have complications and cause both venous and arterial thromboembolisms. Thus, this mechanism could also be considered as an additional reason for higher incidence of ischemic stroke in RCOM patients [20]. In accordance with this hypothesis, in our study we found significant differences between patients with and without AIS in terms of laboratory findings that indicate systemic inflammation [21, 22], including higher level of D-dimer levels, higher white blood cell counts, higher neutrophil to lymphocyte ratios (NLR), lower lymphocyte percentages, and higher BUN/creatinine ratios.

We acknowledge that this study has some limitations that can be addressed in future studies. First, there was a lack of uniform follow-up imaging in performing longitudinal analysis of the imaging findings over the time to find possible prognostic factors of ischemic stroke in ROCM patients associated with CAM. Second, a brain MRI was not performed for a small number of our patients and only brain CT had been performed. Third, we were not able to formally evaluate the severity of COVID-19 manifestations as a possible factor affecting patient prognosis. Nevertheless, we believe that this paper contributes to the early literature and raises awareness of this potentially devastating disorder.

Conclusion

Ischemic stroke is a common consequence of rhino-orbito-cerebral mucormycosis (ROCM) associated with COVID-19 infection. Stroke in the setting of ROCM is not associated with conventional ischemic stroke risk factors. Neuroimaging features including qualitative and quantitative evaluation of the cavernous sinus, internal carotid artery (ICA) and superior ophthalmic vein (SOV) are useful in better understanding the mechanism and risk profile of ischemic stroke in patients with ROCM. The most common pattern of stroke in these patients is watershed infarction. Laboratory findings including higher levels of inflammatory biomarkers can also be associated with stroke in this group of patients. Meticulous and timely evaluation of COVID-19 associated mucormycosis (CAM) patients in terms of neuraxis involvement by having a high index of suspicion and appropriate neuroimaging is crucial to prevent the potentially debilitating consequences.

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Author Contribution MAN analyzed the data, monitored data collection, and drafted and revised the paper. AZ analyzed the data, monitored data collection, and drafted and revised the paper. NR designed data collection tools, monitored data collection, and drafted and revised the paper. HP prepared the statistical analysis plan, monitored data collection, and revised the draft paper. MK initiated the collaborative project, designed data collection tools, monitored data collection, analyzed the data, and drafted and revised the paper. MRN monitored data collection and revised the draft paper. SH designed data collection tools, monitored data collection, wrote the statistical analysis plan, analyzed the data, and drafted and revised the paper. FKH monitored data collection and revised the draft paper. MS monitored data collection and revised the draft paper. AV supervised the data collection, analyzed the data, and revised the draft paper.

Declarations

Conflict of interest M.A. Najafi, A. Zandifar, N. Ramezani, H. Paidari, M. Kheradmand, B. Ansari, M.R. Najafi, S. Hajiahmadi, F. Khorvash, M. Saadatnia and A. Vossough declare that they have no competing interests.

Ethical standards This study was performed in line with the principles of the Declaration of Helsinki. This study was approved by the Institutional Review Board of the Isfahan University of Medical Sciences (IR.ARI.MUI.REC.1400.025). Verbal consent to participate in this study was obtained from all patients or their surrogates by one of the co-investigators.

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