Original Article

Cross-sectional study to describe the severity, bio-chemical associations, and final outcomes of COVID-19-associated rhino-orbital-cerebral mucormycosis in a tertiary hospital of East India

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Purpose: The second wave of coronavirus disease 2019 (COVID-19) pandemic triggered a mucormycosis epidemic in India. Diabetes mellitus and dysregulated immune response were contributors, and rhino-orbital-cerebral mucormycosis (ROCM) was the most common presentation. It is however not known whether bio-chemical parameters at presentation correlate with stage of ROCM or final outcome in terms of vision or mortality. **Methods:** This retrospective, hospital-based study included all in-patients of mucormycosis with ophthalmic manifestations at presentation admitted during June 1, 2021 to August 31, 2021. It aimed to evaluate the association between severity of infection, serum levels of HbA1c, ferritin, interleukin-6 (IL-6), C-reactive protein (CRP), and D-dimer levels at presentation and outcome. **Results:** There were altogether 47 eligible cases having a mean age of 48.8 ± 10.9 years with a male:female ratio of 2.6:1; forty-two (89.4%) had pre-existing diabetes, and five (10.6%) had steroid-induced hyperglycemia. The mean HbA1c among diabetics was 9.7 ± 2.1. HbA1c and serum CRP showed an increase over subsequent stages, which was not statistically significant (P = 0.31). IL-6 values for all stages were similar (P = 0.97). Only serum ferritin levels showed a statistically significant increase over stages (P = 0.04). IL-6 was significantly lower (P = 0.03) in patients who survived, whereas CRP levels were significantly lower in patients who had final visual acuity (VA) better than only perception of light (P = 0.03). **Conclusion:** Uncontrolled diabetes mellitus is a significant association of ROCM. Serum ferritin levels at presentation best correlate with extent of the disease. CRP levels are best to prognosticate cases that will have sufficient VA to carry on activities of daily living, whereas IL-6 levels are best associated with survival.

Key words: COVID-19, glycosylated hemoglobin, immuno-suppression, orbital exenteration, survival, visual acuity

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Globally, prior to the coronavirus disease 2019 (COVID-19) pandemic, the annual prevalence of mucormycosis was estimated to be at 0.02 to 9.5 cases (median = 0.2 cases) per 100,000 persons,[1] whereas the incidence was reported to be 0.005 to 1.7 per million population.[2] Using a computational model, the estimated prevalence was nearly 70 times as much in India (140 per million population).[3] This was attributed to our country having the second largest population in the world with a large number of diabetics. Diabetes mellitus (56%) was the significant risk factor and the most common associated co-morbidity in rhino-orbito-cerebral mucormycosis [ROCM; odds ratio (OR) = 7.55, P = 0.001].[4] A meta-analysis in 2018 found it to be an independent risk factor for the condition with 46% mortality.[2]

The second wave of the COVID pandemic triggered a sudden increase in incidence of mucormycosis, causing it to be declared an epidemic in the country.[5] Till August 1, 2021, 45,374 cases of COVID-associated mucormycosis (CAM) had been reported in India with more than 4300 deaths, and the cases increased to 51,775 till November 2021.[6,7] Severe acute respiratory syndrome coronavirus 2 (SARS-nCoV-2) affects beta cells of the pancreas, thus causing or aggravating hyperglycemia, which was further worsened by steroid therapy used in these cases.[8,9] Hypoxemia, the acidic environment of tissues (diabetic ketoacidosis), background co-morbidities, and dysregulated over-active immune response with elevation in inflammatory markers including C-reactive protein (CRP), ferritin, interleukin-6 (IL-6), and D-dimer have been claimed to contribute to the unusual spurt in cases of mucormycosis.[10–12]

Global data indicate that mucormycosis has carried a case fatality rate ranging from 32 to 70% depending on organ involvement in the pre-COVID era,[13] and 46% survivors end up with life-changing morbidities including vision loss.[14] In June 2021, a classification of ROCM was proposed to assess progression and prognosis of the disease.[15] ROCM has been the most common form of mucormycosis seen in our country.[14]

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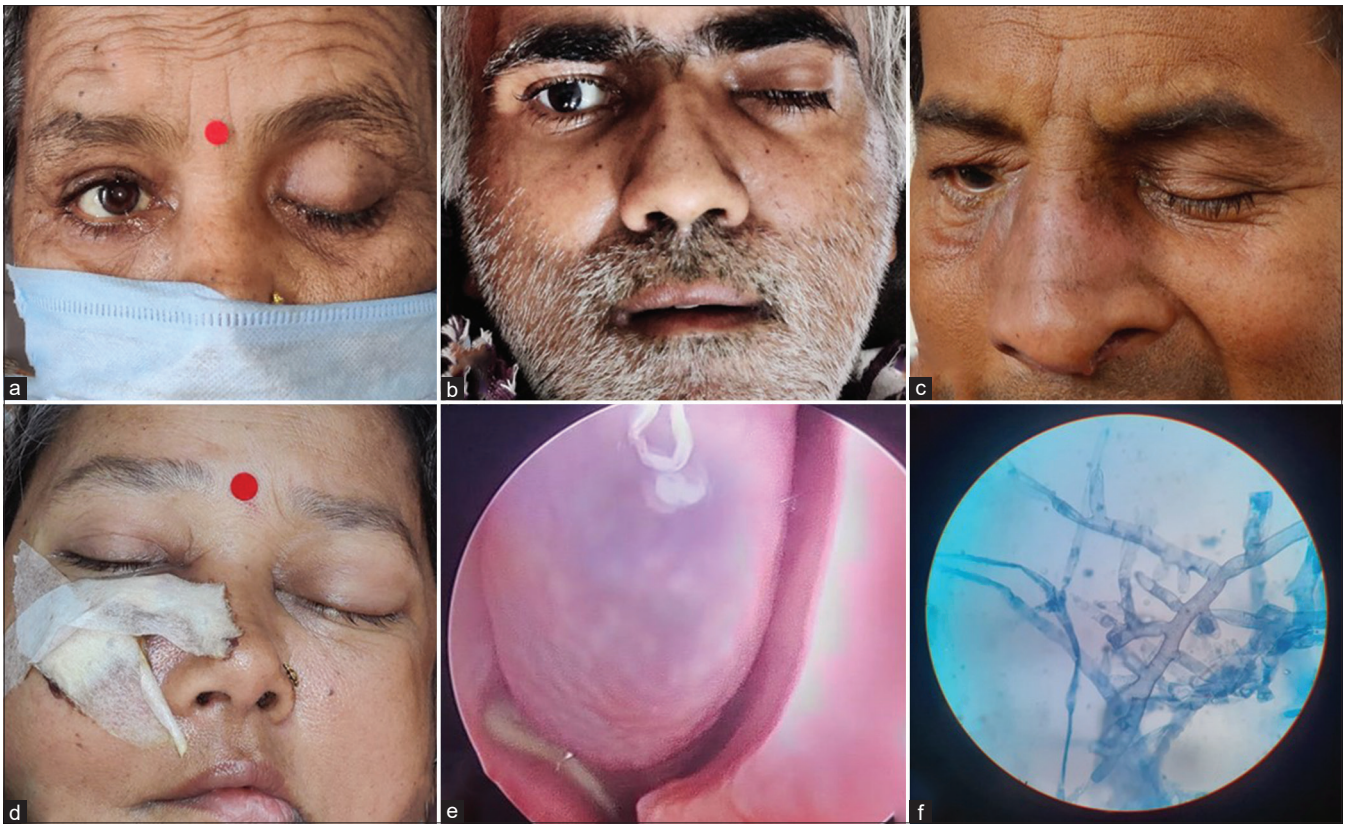

Figure 1: (a) Left-sided ptosis, (b) Left nasal periorbital involvement with ptosis, (c) Bell's palsy with ptosis, (d) Rt Maxillary sinus involvement, left Bell's palsy with bilateral ptosis, (e) Inferior turbinate involvement, (f) KOH mount showing hyphae

COVID-19-associated ROCM (CA-ROCM) has been defined by Muthu *et al*. as that developing between 7 days and 3 months of confirmed COVID-19 infection.[16] It is not known whether the levels of bio-chemical parameters at presentation correlate with the stage of CA-ROCM or the final outcome of these patients in terms of vision or mortality. Hence, the present study was performed to fill this important gap in knowledge. The results of this study could also serve as a guide to prognosticate the disease and plan resource allocation for its management in future.

The present study was aimed to evaluate the association between stages of ROCM and serum levels of HbA1c, ferritin, IL-6, CRP, and D-dimer levels in patients with ophthalmic manifestations at presentation and to analyze the odds of bio-chemical parameters found associated with the final outcomes of interest, namely, visual loss and death.

Methods

Study setting and study period

This was a hospital records-based retrospective cross-sectional study conducted from June 1 to August 31, 2021 at our government tertiary care teaching hospital in Bihar, which had been designated for COVID care and management of post-COVID-related complications. A mucormycosis ward had been established in our institution, where a multi-disciplinary team of ophthalmologists, otorhinolaryngologists, neurologists, and physicians supported by the departments of microbiology, pathology, and radiology collaborated with the hospital administration to manage these patients as per ICMR and state government guidelines.

The study conformed to the tenets of Declaration of Helsinki, and Institutional Ethics Committee approval was obtained.

Inclusion criteria

All patients presenting to our hospital and admitted in the mucormycosis ward with ROCM which conformed to the definition of CA-ROCM[16] and ophthalmic manifestations at presentation [Fig. 1a-e] were included in the study.

CA-ROCM had been diagnosed by positive KOH smear (broad ribbon-like aseptate hyphae, Fig. 1f), culture (growth of Mucorales species on Saboraud dextrose agar) and/or histo-pathological examination (angioinvasion and tissue necrosis), or definite radiological evidence [on magnetic resonance imaging (MRI)/contrast-enhanced MRI of brain, orbits, and paranasal sinuses] in suspected cases which could not be confirmed by micro-biological or histo-pathological examination.

Exclusion criteria

Patients who tested positive for COVID-19 at the time of initial presentation were admitted in the COVID ward where detailed ocular examination at presentation was not possible. Records of such patients were excluded. Non-COVID cases having similar ocular manifestations because of other causes such as sino-nasal myiasis, aspergillosis, candidiasis, Tolosa-Hunt syndrome, or orbital pseudotumor were also excluded from the study.

Study protocol

Hospital records of all eligible patients, which had been retained taking consent for use and storage of their clinical

information and medical images for research purposes, were reviewed. Anonymized information was manually abstracted from these records for the present study.

Data included demographic information related to age and gender, COVID positivity (and testing method), history of diabetes and other co-morbidities, immuno-suppression, history of oxygen supplementation or steroids during treatment received, and bio-chemical parameters including HbA1c, D-dimer, ferritin level, CRP, and IL-6 levels at presentation. Clinical staging of mucormycosis[15] was performed as per relevant clinical information including detailed ocular examination of visual acuity (VA), external eye, slit-lamp bio-microscopy and dilated fundus examination, optical coherence tomographs, B-scan images, photographs, and MRI reports. The normal levels of bio-chemical parameters as set by our institute's clinical laboratory were <6.5% for HbA1c, 0–6 mg/L for CRP, <16.4 pg/ml for IL-6, 12–300 ng/ml for ferritin, and <400 ng/ml for D-dimer.

Final hospitalization outcomes included discharge, in which case the final VA was recorded. Any surgical interventions necessitating removal of the eyeball were also taken note of. In case of death of the patient, final VA achieved prior to the event and the cause of death were documented.

All anonymized data were entered into a worksheet (Microsoft Excel, Microsoft Corporation, USA). Missing data were reported as such.

Statistical analysis

Statistical analyses were performed using the statistical software package IBM SPSS Statistics version 26.0 for windows. The mean, standard deviation, and range were calculated for demographic and bio-chemical parameters wherever appropriate. The Chi-square test was used to compare the proportions of patients with various ocular manifestations and co-morbidities. A *P* value of <0.05 was taken as significant.

Results

Hospital records of a total of 49 patients admitted to the mucor ward during the study period were reviewed. Records of two patients were excluded as they were found to be of sino-nasal myiasis. The mean age of the remaining 47 eligible patients of CAM was 48.8 ± 10.9 years (range 25–69 years). There were 34 males and 13 females (ratio of male:female 2.62:1). The mean period of onset of ROCM from confirmation of their COVID positivity was 19.3 days (range 7–50 days, Fig. 2). Out of these, 18 had documented oxygen therapy during their illness from COVID ranging from 2 to 29 days; 42 (89.4%) were pre-existing diabetics, whereas 5 (10.6%) had steroid-induced diabetes, although 29 (61.7%) patients had received steroid therapy during the course of COVID management. Remdesevir had been used in five (10.6%) cases. Only two patients had good control of the disease, whereas all others 45 (95.8%) were uncontrolled with two having ketoacidosis. The mean HbA1c among diabetics was 9.7 ± 2.1 (range 6.6–15.2). Other co-morbidities were cardiovascular accidents and hypothyroidism in two patients each and cardiac disease, hypertension, liver cirrhosis, and chronic kidney disease in one patient each. HbA1c showed only a slight increase over subsequent stages, which was not statistically significant.

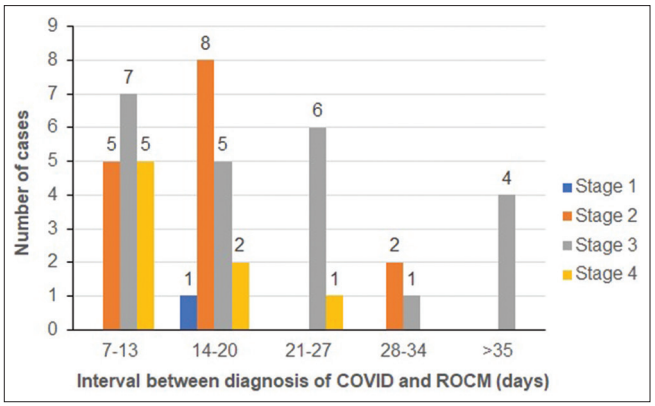

Figure 2: Stagewise distribution of CA-ROCM cases and time elapsed since COVID infection diagnosis

In our study, the mean CRP was 56.7 ± 43.2 mg/L (range 8.8–201.1 mg/ml) and CRP levels were raised in all cases. On considering the stages of CA-ROCM,[15] the levels increased in absolute values over successive stages, which, however, were not statistically significant ($P > 0.05$, Table 1).

The levels of IL-6 were also elevated in all cases with a mean of 49.6 ± 21.9 pg/ml (range 16.9–98.4 pg/ml). Values of IL-6 for all stages except the first did not show significant differences (P=0.97). The mean levels of 71.3 ± 19.0 pg/ml in those who died were significantly more than those in the survivors ($P < 0.05$, Table 2).

Serum ferritin levels in our study were elevated in 41 (87.2%) cases with the mean across all stages being 528.6 ± 272.4 ng/ml (range 87–1371.6 ng/ml). This was the only bio-chemical parameter that showed an increase over successive stages (392.6 ± 190.0, 584.5 ± 286.2, and 628.4 ± 310.2 ng/ml, respectively, in stages 2, 3, and 4), which was statistically significant ($P = 0.04$, Table 1).

Total vision loss was seen in 14 patients, whereas one patient ended up with only perception of light. There were four patients with VA between 20/100 and 20/200, whereas seven patients had VA between 20/40 and 20/100. Twenty-one patients could achieve a final VA of 20/40 or better after treatment. Among bio-chemical marker levels in these patients, only CRP levels were significantly less in patients who ended up with VA better than PL only ($P < 0.05$, Table 2).

The D-dimer values were elevated in 36 (79.6%) cases with mean levels of 617.7 ± 297.8 ng/ml (range 209.6–1680 ng/ml). The level of D-dimer was the highest in stage 1 and showed a lack of statistical significance over successive stages ($P > 0.05$).

Discussion

We report the results of a retrospective single-center cohort study of 47 ROCM patients admitted to the mucormycosis ward of our tertiary government teaching hospital in Bihar during the second wave of the COVID pandemic with the objective of evaluating the association between severity of mucor infection and serum levels of HbA1c, ferritin, IL-6, CRP, and D-dimer levels. Previously in June 2021, the relative frequency of ocular manifestations and risk factors of ROCM in the Indian population were published.[17] In this

Table 1: Description of staging of ROCM and bio-chemical markers (*n*=47)

Stage	*n*	HbA1c	CRP	IL-6	Ferritin	D-Dimer
1a	1	8.4*	16.4*	16.9*	487.2*	987*
Stage 2	15	9.2±1.3	40.8±18.3	49.9±21.5	392.6±190.0	543.4±252.5
2b	11	9.7±1.3	42.3±20.4	48.0±21.5	405.3±220.8	534.9±245.9
2c	4	8.5±1.1	36.4±11.8	55.1±23.7	357.5±62.2	566.6±308.1
Stage 3	23	10.0±2.4	62.1±41.4	50.9±21.6	584.5±286.2	586.1±255.2
3a	9	9.7±2.3	61.8±44.5	42.3±18.3	474.7±324.3	603.4±369.6
3c	12	10.2±2.6	66.3±43.6	53.9±19.8	583.0±190.5	513.9±192.6
3d	2	9.9*	41.8±17.2	72.1±37.3	622.3±193.3	811.5±94.1
Stage 4	8	10.3±3.1	75.8±69.8	49.1±24.8	628.4±310.2	801.7±421.1
4a	2	7.7*	40.6±2.0	55.4±44.6	461.0±434.2	491.5±232.7
4c	6	11.5±3.0	87.6±78.5	47.0±21.0	684.2±286.6	905.2±431.4
H**			2.32	0.06	6.40	2.54
*P***			0.31	0.97	0.04	0.28

**n*=1, **Kruskall–Wallis test performed between stages 2, 3, and 4

Table 2: Outcome and bio-chemical markers of ROCM patients (*n*=47)

Outcome	*n*	HbA1c	CRP	IL-6	Ferritin	D-Dimer
VA PL only or PL neg	15	10.78±2.42	72.79±50.78	54.28±21.58	599.25±229.52	628.12±359.48
VA better than PL	32	9.11±1.65	48.34±36.81	47.16±22.08	492.20±288.77	612.32±267.00
*t**			-1.89169	-1.05498	-1.28576	-0.17053
*P**			0.03249#	0.14853	0.10255	0.43268
Died	5	10.33±2.68	39.59±9.52	71.27±19.04	652.76±259.11	728.06±225.31
Survived	42	9.65±2.07	58.69±45.17	47.00±20.99	513.87±273.11	604.56±304.78
*P***			0.60306	0.0251	0.27572	0.20766

VA=Visual acuity, PL=Perception of light, neg=negative. * Independent Samples *t*-test with one-sided hypotheses, ** Mann–Whitney *U* test. #Cohen's d=0.55 (Moderate effect size); Glass's delta=0.66; Hedges' g=0.58

multi-centric, pan-India study, diabetes mellitus was found to be uncontrolled in 41% of cases. It did not, however, report data on bio-chemical status of serum ferritin, IL-6, CRP, and D-dimer levels at presentation. Also, this study could not include data from our state, probably because the second wave of COVID and the subsequent peak of mucor epidemic occurred here much later than the rest of the country, although 842 cases were treated in Bihar in 2021.[7,18]

In our cohort, the mean age of patients, range, and male:female ratio were comparable to those found by other workers.[19–25]

Diabetes has been described as the most common co-morbidity for CAM in several studies.[19,24–26] The COVID virus itself directly disturbs the integrity of beta cells of pancreas.[9,27] Steroids increase blood sugar levels in known diabetics, leading to loss of control and ketoacidosis, as well as precipitate the disease in pre-diabetics. Diabetic ketoacidosis causes an increase in free-iron concentration and a decrease in serum anti-fungal factors, thus predisposing to fungal infections.[28–30] Improper corticosteroid use has been identified as an independent risk factor for CA-ROCM in Indian eyes.[31] Steroids also reduce the phagocytic activity of white blood cells. COVID-19-induced endothelial damage, thrombosis, and reduced CD4 and CD8 count predispose to opportunistic fungal infection. Low pH in acidosis provides fertile media for mucor spores to germinate. Thus, diabetes and rampant use of corticosteroids in a background of COVID-19 appear to increase mucormycosis.[32] This was evidenced in our series as all patients were diabetic, 89.4% with pre-existing diabetes and 10.6% having steroid-induced hyperglycemia. The majority (about 96%) of these were uncontrolled; however, the HbA1c values did not show a statistically significant increase over subsequent stages, implying that the degree of lack of control did not influence the extent of disease. Other studies from our country have reported similar findings,[18,19,22,23,26] whereas the largest pan-India collaborative study found diabetes mellitus in 78% of patients, which was uncontrolled in a significantly lower proportion (41%) of cases.[17] This may be because of regional differences in health monitoring and health-seeking behavior among patients.[18]

COVID-19 causes a hyper-inflammatory state because of cytokine storm, and increased levels of bio-markers have been associated with a poor outcome in COVID-associated mucormycosis.[33,34] Hyperglycemia leads to glycosylation of transferrin and ferritin, reducing iron-binding capacity and hence causing increased free-iron availability. COVID-19-induced inflammatory cytokines, especially IL-6, increase ferritin synthesis and decrease iron transport. Acidosis too contributes to this by reducing iron-chelating capacity of transferrin.[31] Thus, ketoacidosis-induced free-iron availability also favors growth and dissemination of mucormycosis.[11] In addition, elevated IL-6 itself can worsen insulin resistance[27] and induce nuclear chromatin extra-cellular trap of neutrophil (NET) formation. Hyperglycemia also activates neutrophils to release NET, which causes endothelial injury and promotes venous thrombosis.[35–37]

All these inter-related factors cause proliferation and extensive dissemination of the common commensals of nasal mucosa, with mucormycetes resulting in ROCM.[21]

These observations were exemplified in our study as inflammatory markers were raised in the majority of cases. Of these, CRP levels were raised in all cases, signifying an acute inflammatory response to previous COVID infection. This inflammatory marker showed an increase in absolute values over subsequent stages, which was, however, not statistically significant. Elevated CRP levels have been reported in the majority of patients in studies from all parts of our country, showing means ranging from 47.2 ± 53.4 mg/L to 680 ± 34.4 mg/L.[19,22,23] Although CRP levels at presentation were elevated significantly in patients with decreased final VA in our study, visual improvement cannot be predicted on the basis of CRP levels alone as there can be other contributing factors for vision loss in such patients.

IL-6 levels were also increased with mean levels similar to those observed in another study.[38] However, the levels for all stages were not significantly different. In our study, the mean level of IL-6 in patients who died was 71.3 pg/ml, which is concurrent with a similar study from South India that found levels significantly greater than 70 pg/ml in patients who died of COVID-19.[27] In another study of COVID-19 cases, IL-6 has been found to differentiate non-survivors from survivors with 100% sensitivity and 70.2% specificity.[39]

Mean serum ferritin levels in our study were elevated in 89% cases. This was found to be the only inflammatory marker, the levels of which showed a statistically significant increase over stages. In other studies, higher mean ferritin levels were found, although they were not correlated with the extent of disease.[24,32] It is known that hyperferritinemia in COVID-19 leads to suppression of B- and T-lymphocyte proliferation, which predisposes to mucormycosis.[40] Increased levels of ferritin and decreased iron transport cause increased availability of intra-cellular iron, which in turn upregulates endothelial receptor glucose-regulated protein-78 (GRP-78) and spore coating homolog protein (Cot-H) of mucorales. Hyperglycemia, glycosylation of ferritin and transferrin, and coexisting acidosis all contribute to the same effect, leading to increased susceptibility of the host to progressive mucormycotic invasion.[32]

D-dimer leads to enhanced endothelial dysfunction, platelet aggregation, and widespread micro-thrombi, encouraging propagation of angioinvasive mucorales.[41] Elevated D-Dimer levels have also been observed in other studies.[19,22,24,42] In our study, although these were elevated in about 80% cases, they did not show any significant difference with either the extent of disease or the final outcomes of vision or mortality.

Our study is not without limitations because of its single-centric and retrospective nature with a small sample size. Long-term follow-up of discharged patients could not be taken up to rule out possibility of recurrence or death. Lastly, statistical analysis of levels of bio-chemical markers corresponding to extent of the disease had to be limited to stages 2, 3, and 4. Although levels of the bio-chemical markers are likely to vary with the severity of COVID-19, treatment, and the duration of the disease, markers at the time of diagnosis of COVID-19 were not available for comparison as most cases were referred in from other institutions without proper records. Moreover, repeat tests to document changes in levels of the markers over the duration of their stay in our hospital had not been performed and hence could not be documented in our observations.

Conclusion

A search of published literature found few comparable studies that correlated the extent or severity of CA-ROCM with level of inflammatory markers at presentation. In fact, bio-chemical parameters have been scarcely reported or excluded from analysis in most of them. This study attempted to fill this important gap in knowledge. It has been found that serum ferritin was the most significant marker to correlate with extent of the disease, serum CRP <50 mg/L correlated with preservation of functional VA in patients, and serum levels of IL-6 were significantly >70 pg/ml in patients who died because of CA-ROCM coupled with their co-morbidities.

Thus, our study can serve as a guide to correlate important ocular manifestations and quantitative bio-chemical parameters for a better in-depth analysis of severity of CA-ROCM. It adds to existing knowledge on this topic which can be instrumental in developing clinical guidelines and study protocols in future.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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