Original Article

Assessment of clinical and histopathological characteristics in COVID-19-associated mucormycosis (CAM) patients correlating with outcome: A hospital-based cross-sectional study

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Abstract

Background: The second wave of the COVID-19 pandemic led to a very dreaded complication of mucormycosis. Immunosuppressive action of the COVID-19 virus, co-morbidities, for example, diabetes mellitus (DM), hypertension, use of steroids, and humidified oxygen, are among the important factors that make the patients susceptible to developing mucormycosis. **Objective:** The present study was conducted to identify and understand all the significant histological changes including the type and extent of tissue involvement, the pattern of inflammation, the volume of fungal hyphae, hemorrhage, etc., in patients with COVID-19 associated mucormycosis (CAM) and correlate with clinical outcome. **Method:** It was a retrospective cross-sectional observational study involving all the patients of CAM, who underwent debridement or biopsy over a period of 5 months, from April 01, 2021, to August 31, 2021. CAM was classified based on the radiological evaluation, clinical features, and organs involved. Different demographic, clinical, laboratory, and histologic parameters were recorded. The variables were assessed for their association with poor clinical outcomes using multiple logistic regression. $P < 0.05$ was considered statistically significant. **Results:** A total of 146 patients were included in the study with a mean age of 49.4 years and 71.2% were male. Sino-naso-palatal was the most common type of CAM (32.9%), while sino-naso-cerebral was the least common (14.3%). DM was present in 54.1% of patients, out of which 26.6% were recently diagnosed. The death occurred in 21.9% of patients. Maximum mortality was observed in CAM of sino-naso-cerebral involvement (42.9%). Total leucocyte count (TLC) [OR = 0.87; 95%CI: 0.76-0.97; $P = 0.02$] and C-reactive protein (CRP) [OR = 0.97; 95%CI: 0.96-0.99; $P = 0.008$] were significantly associated with poor outcomes. Other factors, that is, high prothrombin time, DM, ferritin, and the involvement of muscle, skin, and cartilage, were also associated with poor clinical outcomes but were not statistically significant. Similarly, high fungal volume and the presence of thrombosis were also associated with poor outcomes but were not statistically significant. **Conclusion:** CAM more commonly affects males with co-morbidities. TLC and CRP were significantly associated with poor outcomes. Histologically, the involvement of skin, muscle, and cartilage and the presence of excessive fungal hyphae and thrombosis were also associated with poor outcomes.

Keywords: Co-morbidities, COVID-19 virus, Indian subcontinent, mucormycosis, pandemic

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Introduction

The COVID-19 pandemic during the second wave was more devastating and put the entire world in turmoil with India among the top countries encountering the highest caseload. Although the pandemic was controlled for a few months (mid of February 2021 to the end of June 2021), this time it led to several persisting co-morbidities among which mucormycosis infection was one of the most severe consequences leading to morbidity and mortality.

Mucormycosis (previously called zygomycosis) is the term used to name invasive fungal infections caused by saprophytic environmental fungi, belonging to the subphylum *Mucoromycotina*, order *Mucorales*.[1] Mucormycosis is very dreadful in comparison to malignancies and other infectious diseases as it causes necrosis and destruction of any body tissue such as skin, blood vessels, nerves, cartilage, muscle, bone, etc., and spreads very fast to involve adjacent organs due to its property of angioinvasion and neural invasion. There are only a limited number of studies describing histopathological features in COVID-19-associated mucormycosis (CAM). We have planned this study to determine the histological pattern of mucormycosis associated with COVID-19.

Mucormycosis is an opportunistic fungal infection caused by mucor hyphae, which are commonly available in humid air, soil, plants, dung, rotting fruits, and vegetables. Any conditions causing immune suppression, such as diabetes, organ transplant, hematological malignancies, steroids, increased iron metabolism, and intra-venous drug use, increase risk of mucor infection. Rhino-orbito-cerebral form of mucormycosis is more prevalent in diabetic patients. COVID-19 virus-associated immune suppression with pre-existing co-morbidities, such as diabetes mellitus (DM), hypertension, and its therapeutic management like O_2 support, steroids, antibiotics, immnosuppressants, etc., have made the patients susceptible to secondary infections, such as mucormycosis.[2] Steroids shoot the blood sugar levels, particularly in diabetic patients, and also cause an acidic environment that favors fungal growth.

Mucormycosis is caused by the inhalation of its filaments (hyphal form), particularly in patients with a compromised arsenal of immune defense. The fungal hyphae attack the blood vessels, causing angioinvasion and angiodestruction, resulting in tissue infarction, necrosis, and thrombosis.

Mucormycosis survives in the host by evading the immune system and surviving inside the host cell and perturbing the immune system further damaging the host cell.[3] COVID-19 infection acts as a trigger for mucormycosis in co-morbid conditions, such as diabetes, malignancies, and organ transplants. Moreover, some patients without a history of any underlying co-morbid conditions were also diagnosed with mucormycosis, post-COVID-19 infection.[4] Although the exact mechanism of mucormycosis as post-COVID complication is not validated, many plausible explanations can be implicated. COVID-19 patients exhibit a wide array of pulmonary changes which may act as a focal point for fungal initiation.[5,6] Furthermore, COVID-19 causes immune dysfunction preventing the neutrophilic phagocytosis from engulfing and clearing the fungal spores upon entry.[7] COVID-19 patients requiring a prolonged hospital stay, ICU care, and mechanical ventilation were more susceptible to mucormycosis. In some hospitals, industrial oxygen was also used to fulfill high oxygen demands. The occurrence of fungal spores in humidifier chambers, and ventilators also contributed to mucormycosis.

COVID-19 virus, particularly in uncontrolled diabetic patients treated with steroids leads to hyperglycemia and alteration in iron metabolism. Also, immune suppression due to steroids and DM leads to the release of abundant iron by sequestering proteins, which creates a favorable environment for the growth of fungi. Moreover, high iron concentrations release reactive oxygen species damaging different tissues in mucormycosis.[2]

Mucormycosis in COVID-19 patients shows a varied spectrum of pathological changes depending upon the extent of immunosuppression, blood glucose levels, and other co-morbidities.

The angio-invasive properties of the fungus are the principal mechanism responsible for the different histological changes. The fungal hyphae cause angioinvasion, angiodestruction, and thrombosis of blood vessels, which leads to tissue ischemia and necrosis as well as involvement of adjacent organs.

Understanding the pathogenesis of CAM is very important for the practice of primary care physicians. We undertook this study mainly to understand the factors responsible for mucor infections on scale of an endemic in the backdrop of COVID-19 infection, different histological changes, and their relations with the outcome. Although the endemic is over now, an in-depth knowledge of pathogenesis will provide important insight into the primary physician to face any similar future challenges.

Materials and Methods

This is a retrospective cross-sectional observational study involving all the patients suffering from CAM who underwent debridement or biopsy at our institute over a period of 5 months, from 1 April 2021 to 31 August 2021. An ethical approval was taken from the Institutional Ethics Committee vide letter no. 1970/IEC-AIIMSRPR/2021. The demographic details, COVID history, and other clinical details were obtained from the patient requisition form, while laboratory details were noted from the hospital information system. The slides were reviewed thoroughly, and the following histopathological details were noted as per the protocol [Table 1]. Special stains, Periodic Schiff (PAS) and Gomorimethanamine silver (GMS), were evaluated for confirmation of Mucor.

At the time of admission, all the patients were subjected to radiological evaluation by magnetic resonance imaging (MRI)

Table 1: Various histological parameters evaluated in the study

Parameters	Interpretation
Volume of fungus	• High volume ≥10 fungal hyphae/hpf • Low volume <10 fungal hyphae/hpf
Vascular changes	Angioinvasion, Angiodestruction, Thrombosis, Obliteration, Vasa vasorum involvement
Types of inflammation	Acute, Chronic, Mixed, Granulomatous
Extent of necrosis	• High >20% tissue in total no. of blocks • Low <20% tissue in total no. of blocks
Eye involvement	Optic nerve, Extra-ocular muscles, Soft tissue, Cornea/Sclera, Orbital bone
Tissue involved	Nerve, Skeletal muscle, Cartilage, Skin, Bone, Periodontal tissue,
Co-infections	Other fungus, bacterial colonies

and/or contrast-enhanced computer tomography (CECT) for staging along with routine investigations (complete blood count (CBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), lactate dehydrogenase (LDH), ferritin, HbA1c, coagulation profile, fasting and postprandial blood sugar levels, lipid profile, and KOH preparation) as per the hospital protocol. The patients were classified into different clinical-pathological stages taking into account radiological findings, the extent of clinical involvement, pathological reports, and Hanavar classification system guidelines.[8] A multidisciplinary team evaluated each patient and performed debridement of the necrotic tissue subsequently followed by antifungals as per the standard protocol. The patients were started on injection of liposomal Amphotericin 3 mg/kg body weight on a clinical basis following the KOH positive report for fungi demonstrating broad aseptate hyphae. A cumulative dose of 2.5-5 g was given depending on the extent of involvement followed by discharge of the patient on tablet Voriconazole for 3 months. CAM was defined as a patient with a documented history of COVID-19 infection presenting with clinical and radiological features of mucormycosis which on KOH mount or histopathological examination of debrided tissue or nasal swab revealed mucor. A detailed histopathological evaluation was done by two pathologists including multiple variables. The variables considered were fungal load, vascular changes, type of tissue involved, type of inflammation, amount of necrosis, and hemorrhage [Figure 1]. In eye involvement cases, parts of the orbit affected were also analyzed. Vascular changes were analyzed meticulously involving features, that is, angioinvasion, angiodestruction, obliteration, thrombosis, and vasa vasorum involvement [Figure 2]. The data have been presented as descriptive statistics, that is, frequencies, percentages, mean, and standard deviation, as appropriate. The data have been presented as mean or percentage for continuous or categorical data. Multiple logistic regression was used to analyze the association between factors affecting poor clinical outcomes among patients of CAM, and a $P < 0.05$ was considered statistically significant. Death was considered poor clinical outcome, while patients surviving following surgery/drug therapy were defined as a good clinical outcome.

Results

A total of 146 patients were included in the study. The mean age was 49.4 years, the majority of them were in between fourth and fifth decade of life (80.8%). DM was the most common (54.1%) co-morbidity followed by concomitant DM and hypertension in 25.3% of patients. Among 79 patients with a history of DM, 21 had recent onset (<6 months), and similarly 11 of 37 hypertensive patients had a history of recent onset (<6 months). The level of HbA1C among diabetics was ranging from 5.1 to 13.7. Paranasal sinuses with or without the nasal cavity were the most commonly involved organs, while orbit and brain were involved in 30.8% and 14.4% patients, respectively [Figure 3]. Most of the patients showed raised levels of inflammatory markers ESR, CRP, and ferritin, of which ferritin and CRP showed a relation with the poor outcome, with CRP being statistically significant ($P = 0.008$) [Table 2]. Total leucocyte counts also showed a statistically significant relation with the poor outcome ($P = 0.02$). Among other parameters investigated like coagulation profile, lactate dehydrogenase (LDH), lipid profile, D-dimer, blood sugar levels, and HbA1c, except for high prothrombin time, none showed a relation with the outcome. The histological findings, that is, fungal load, vascular changes, type of tissue involved, type of inflammation, amount of necrosis, and hemorrhage, were studied thoroughly, of which skeletal muscle and skin involvement showed statistically non-significant relation with the outcome [Figure 4].

Most cases (87%) showed high fungal volume, some of which also revealed mixed fungal infections. Bone (70%) was noted as the most commonly involved tissue followed by the nerve. Mixed inflammation (69.9%) was frequently noted, while granulomatous inflammation was common in cases with muscle involvement. Hemorrhage, necrosis, and granulation tissue formation were the frequent pathological changes. In all but one patient with eye involvement the optic nerve margin was positive suggesting fungal extension possibly involving the brain [Figure 3d]. At 6 months of follow-up, 114 patients (78.1%) showed disease-free survival, while 32 (21.9%) succumbed to the disease. Maximum mortality was observed in CAM of sino-naso-cerebral involvement (42.9%).

Discussion

The COVID-19 virus in association with DM, irrational use of steroids, antibiotics, long-term intensive care unit admission, and ventilator support together lead these patients susceptible to opportunistic fungal infection popularly known as CAM. SARS-CoV-2 virus causes alteration in cell-mediated immune response preventing the clearing of the fungal spores.[9] Moreover, COVID-19 infection causes a marked increase in the acute phase reactant CRP, ESR, and ferritin. The ferritin, an iron analog, promotes mucor growth, which requires an iron-rich environment.[10] In this study, serum ferritin was raised in 92.4% of patients ranging from 165 to 1650 ng/ml. Furthermore, in patients with diabetic ketoacidosis, due to low serum pH, ferric

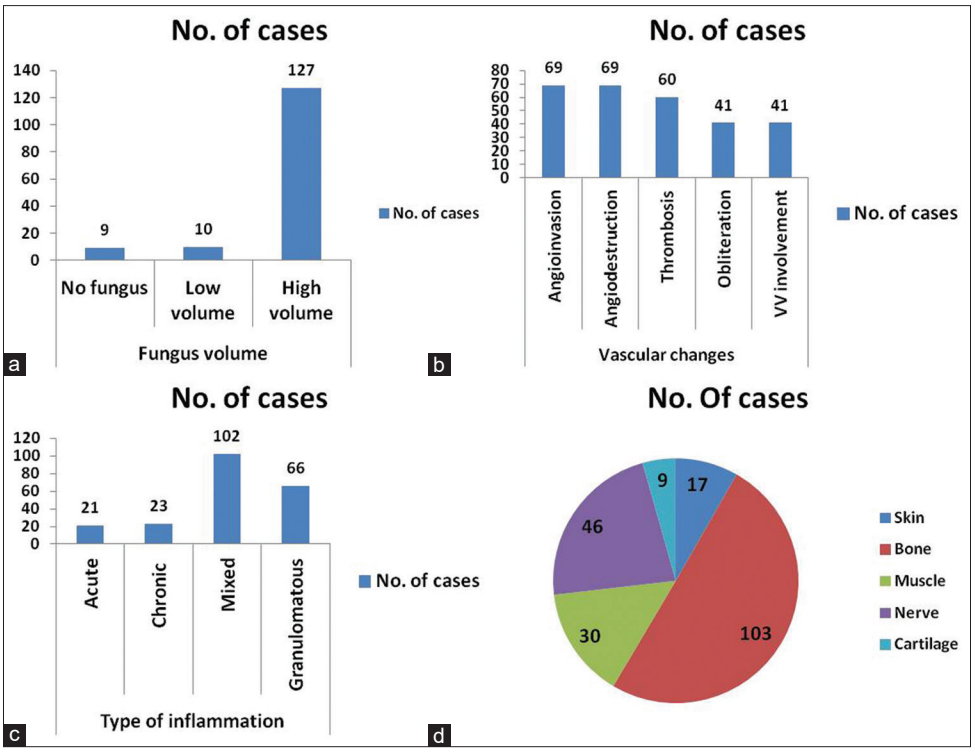

Figure 1: Analysis of different histological parameters: (a) Fungal volume, (b) type of vascular changes, (c) type of predominant inflammation, and (d) type of tissue involvement

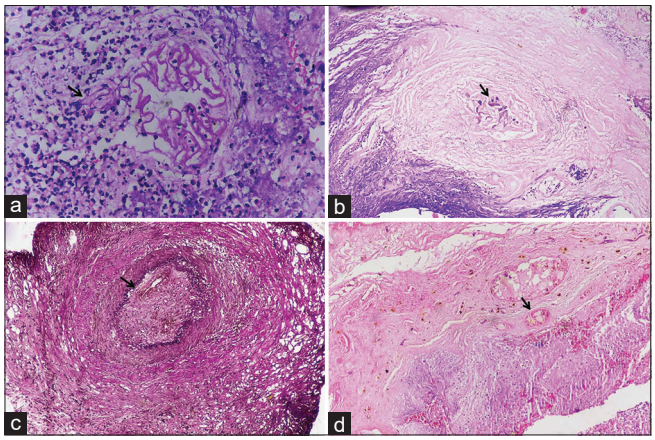

Figure 2: Histological images showing different vascular changes: (a) Angioinvasion (arrow) (H and E ×100), (b) angiodestruction (arrow) (H and E ×40), (c) vascular obliteration (arrow) (VGE ×100), and (d) vasa vasorum involvement (arrow) (H and E ×40)

Table 2: Factors affecting survival in mucormycosis

Factor	Odds Ratio, 95% Confidence Interval	*P*
Age	1.021 (0.93–1.11)	0.62
Sex (female)	4.31 (0.83–33.05)	0.10
Diabetes mellitus	0.43 (0.07–2.02)	0.30
Prothrombin time	0.80 (0.54–1.25)	0.30
Activated partial thrombin time	0.98 (0.95–1.00)	0.19
Total leukocyte counts	0.87 (0.76–0.97)	0.02
ESR	1.00 (0.98–1.02)	0.58
CRP	0.97 (0.96–0.99)	0.008
Ferritin	0.99 (0.99–1.00)	0.74
LDH	1.00 (0.99–1.00)	0.68
HbA1C	1.18 (0.87–1.65)	1.05
Involvement of muscles	0.53 (0.18–1.66)	0.26
Involvement of cartilage	0.38 (0.06–2.10)	0.26
Involvement of skin	0.56 (0.15–2.25)	0.39
Involvement of bone	1.70 (0.34–12.68)	0.54
Presence of osteomyelitis	0.98 (0.13–4.63)	0.99
Volume of fungus	0.42 (0.02–2.65)	0.44
Presence of angio-invasion	1.14 (0.24–8.19)	0.15
Presence of thrombosis	0.84 (0.10–4.54)	0.85
Presence of vascular obliteration	1.22 (0.37–3.95)	0.73

iron is released from transferrin, which also contributes to the iron-rich environment. DM was noted in 54.1% of patients, and many of them presented with uncontrolled blood sugar levels, which were further worsened by steroid treatment.

A peculiar finding observed in this series was the presence of high fungal volume (87% cases), irrespective of predisposing factors such as diabetes, history of steroid treatment, immunosuppressive drugs, hypertension, and ventilator support during COVID-19 infection. We have defined high fungal volume as ≥10 fungal hyphae/hpf. It is assumed that the angioinvasive and neurotropic properties of the fungus along with the inflammatory milieu, COVID-19-related immunosuppression supported by high serum iron concentration is responsible for the rapid proliferation of mucor. Only nine patients did not reveal fungus in the biopsy;

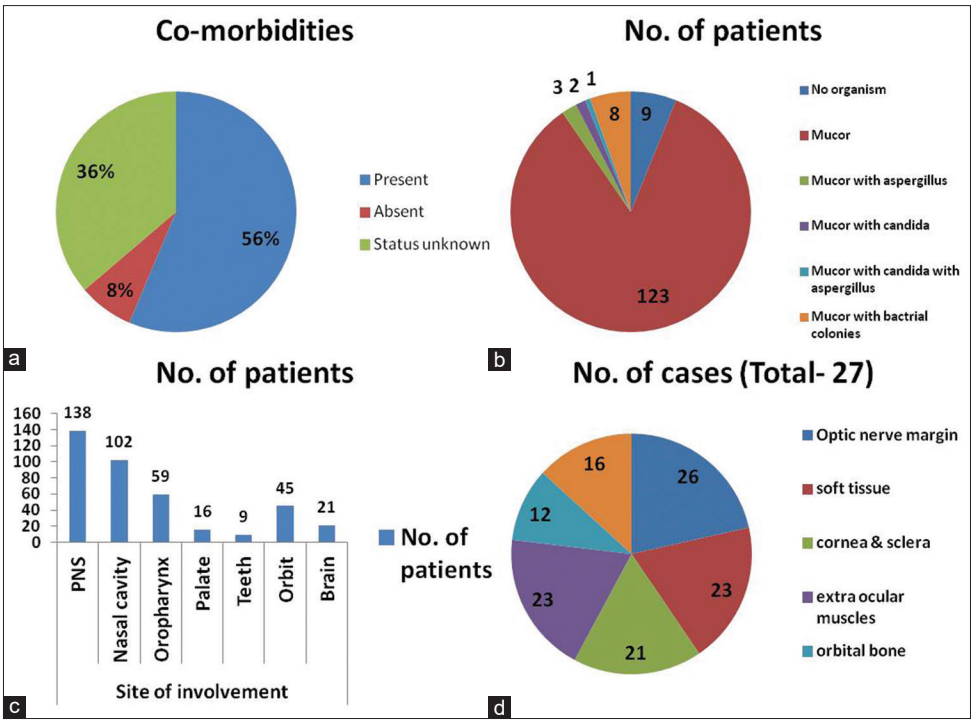

Figure 3: Clinical profile and orbital pathology evaluation: (a) presence of co-morbid conditions, (b) type of micro-organisms, (c) site of involvement, and (d) parts of orbit involved

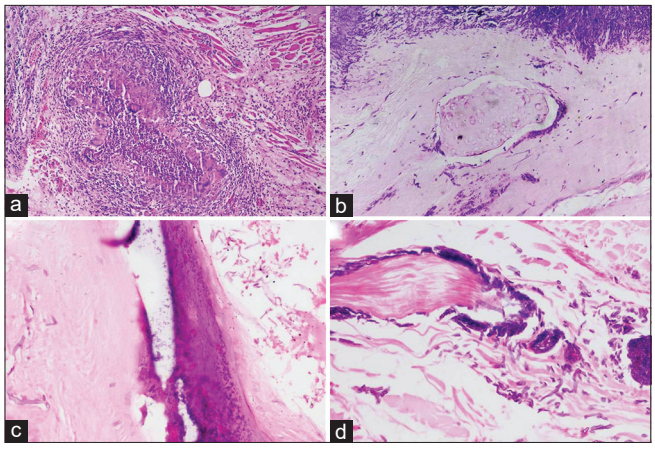

Figure 4: Representative histological images, showing (a) muscle invasion with granulomatous inflammation and giant cells, (b) cartilage, (c) bone, and (d) nerve involvement (H and E ×100)

however, their diagnoses were based on KOH preparation and characteristic clinical presentation.

Histologically, most cases are also characterized by the presence of large areas of necrosis, granulation tissue, and varying degrees of hemorrhage.

Extensive utter invasion of all the tissues irrespective of their density by mucor accompanied by vascular alterations like angioinvasion, angiodestruction, and thrombosis is the hallmark of CAM. Angioinvasion not only leads to infarction of the tissue due to ischemia but also accelerates the dissemination of the mucor to rapidly involve adjacent structures. Interestingly, we have evaluated all the vascular changes and found that mucor not only causes angioinvasion but also causes angiodestruction, thrombosis, vessel obliteration, and involvement of vasa vasorum in medium- and large-sized vessels. In this series, we found angioinvasion and angiodestruction in 47.2% of cases, which is much lower in comparison to the 83.33% reported by Sravani *et al*.[11] in their study of 30 patients. However, sampling may be an important cause for the variation in the results. Thrombosis was noted in 41% of the samples, which likely resulted from the activation of the coagulation cascade due to an inflammatory event caused by the fungus. Thrombosis and activation of the coagulation cascade are further supported by raised PT, aPTT, and D-dimer levels in 19.8%, 42%, and 58.6% of patients, respectively. Vascular obliteration was seen in 28% of the specimens, which is explained by multifactorial events like active atherosclerotic phenomenon, particularly in diabetic patients, deranged lipid profile (40%), smooth muscle proliferation due to inflammation and high volume of fungal hyphae itself compromising the luminal space. High fungal volume was reported in 87% of the biopsy samples. An important observation that we noticed was the direct invasion of the vasa vasorum causing ischemia of medium and large vessels, which further jeopardized the blood supply of the affected tissue, hence accelerating infarction.

The predominant type of inflammatory reaction varies from case to case in CAM. We found mainly mixed inflammatory reactions in a majority (69.9%) of the cases followed subsequently by chronic inflammation (15.7%) and acute inflammation (14.4%). Additionally, granulomatous inflammatory response was noted in

45.2% of the cases particularly more prevalent in skeletal muscle involvement. Sravani *et al*.[11] reported acute inflammation in 83.33%, and granulomatous inflammation in 10% of the cases; however, no inflammation was found in 6.67% of cases.

Another important mechanism of dissemination of the mucor is via perineural invasion. In this series, we noted perineural invasion in 31.5% of the cases, most of which (93.5%) also showed intraneural invasion. The proportionate number of cases with perineural invasion is much lesser in comparison to previous studies in which it was ranging from 72% to 90% of the cases.[11-13] An interesting observation with respect to the perineural invasion noticed was the involvement of the optic nerve margin in all but one (26/27) patients who underwent exenteration. It signifies that brain involvement in CAM is facilitated by perineural invasion, particularly via the optic nerve. Also, most of the patients with gross eye involvement are likely to have brain invasion irrespective of the presence of frank symptoms or radiological changes. However, the optic nerve is not the sole route for brain involvement in CAM. Different hypothetic mechanisms are proposed for perineural invasion in several malignancies like paracrine signaling between tumor, nerve and stromal cells, upregulation of neurotropic and axonal molecules, and low resistance property of nerve sheath conduit promoting tumor cell growth.[14,15] These mechanisms might also have an important role in CAM for spreading along nerve bundles.[16] However, it needs to be validated and provide a great opportunity as well as a challenge to explore the pathogenesis of mucormycosis particularly perineural invasion. Perineural invasion is one of the most significant pathological parameters, which directly correlates with the outcome. However, in this study, a significant relationship is not found between perineural invasion and survival. Brain invasion was reported in 14.4% of patients who were managed by debridement of necrotic tissue by a neurosurgeon. The bone invasion was a very frequently noted histological finding seen in 70.5% of samples, 19.9% of which showed an osteomyelitic pattern of inflammation. All the cases (20.5%) with skeletal muscle involvement showed a granulomatous reaction. Cartilage (6.16% cases) was noted as the most resistant tissue for mucor invasion; however, this may be pertaining to tissue sampling.

In some patients, dual fungal infections or superadded bacterial infections were also noted, which were further confirmed by microbiological culture.

We found a relatively low mortality rate of 32/146 (21.9%) in this study in comparison to other similar studies from across India. Choksi *et al*.[17] reported 53% mortality at day 21 from a cohort of 73 patients. Vare *et al*.[18] included 67 CAM patients and reported a mortality rate of 38% on day 20. Dave *et al*.[19] reported outcomes from 58 patients of CAM and found a mortality rate of 34%. Walia *et al*.[20] reported a lower mortality rate of 10% in a large sample of 540 cases of CAM.

The variation in the outcome reported in different studies appears to be multifactorial and may not represent true values. As many centers faced scarcity of liposomal amphotericin due to limited supply, different treatment protocols (endoscopic vs. open sinus debridement), tertiary healthcare centers with multidisciplinary approaches vs. primary and secondary healthcare centers and inadequate follow-ups are some of the important confounders observed in these studies.

Though, previously several papers describing CAM have been published; however, none of them described histological changes in detail, which is very important to understand the pathogenesis of this dreaded endemic in a pandemic leading to vast morbidity and mortality.

Conclusion

CAM is more prevalent in elderly males and frequently associated with co-morbidities. Serum ferritin elevated in most patients might play a pivotal role in mucor proliferation. Extensive vascular changes and neurotropism are important mechanisms for fungal spread. High fungal volume irrespective of co-morbidities in most patients is a result of the pathogenic properties of fungus, high iron concentration, and immunosuppression, which require further research for validation. All the patients with eye involvement show frequent optic nerve margin invasion hence should be aggressively treated for possible brain involvement. The pathologists should examine the slides carefully to rule out mixed fungal or con-commitment bacterial infections as they bear direct therapeutic implications.

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Conflicts of interest

There are no conflicts of interest.

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