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Risk factors for palatal and orbital involvement in mucormycosis epidemic–Report of a center in India

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ABSTRACT

Background: Mucormycosis of the nose and paranasal sinuses has emerged as an epidemic following COVID-19 pandemic. The management involves surgical debridement, the extent of which depends on the bulk of the disease. Extension to the orbit and palate depends on the involvement of specific sites in the nose and paranasal sinuses. This study intended to identify those sites.

Materials and methods: This was a single-center case-control study. There were 3 groups according to the region involved (Palate, orbit and both). The fourth group with neither involvement was the control. Scoring system was used to estimate the bulk of disease according to the site involved in MRI scan. Odds ratio and chi-square tests were used to study risk and association respectively. ROC curve was obtained for the MRI scores of the cases and controls.

Results: 214 patients were studied in all; 44.39% and 61.68% had palate and orbit involvement, respectively. Maxillary sinus roof had significant association and the highest risk for spread of disease into the palate. The risk for the orbit to be involved was increased when there was disease in the cavernous and sphenoid sinus. For the orbit, the site with the significant association was the ethmoid sinus, infratemporal fossa and roof of the maxillary sinus.

Conclusion: Due attention should be given for clearance during surgical debridement to the high-risk sites to prevent recurrences and reduce morbidity and mortality. MRI scores were most helpful to identify the bulk of disease when both palate and orbit were involved.

1. Introduction

Rhino-orbital Mucormycosis cases have emerged as an epidemic within the pandemic of COVID-19 in India and a few other nations. The majority of the patients have involvement of palate, orbit or both adding to the bulk of the disease thereby increasing the morbidity and mortality. The surgeries are extensive and mutilating when they are involved; hence there is a need to determine what leads to palatal or orbital extensions from the nose and paranasal sinuses so that these critical structures might be addressed better during debridement. It is difficult to predict the progressive course of the disease and the extent of involvement of the vital structures in the vicinity of the primary disease that might finally decide the fate of the patient. This spread directly affects the debridement clearance required in the patients.

This study intended to identify the involvement of critical structures that may lead to the extension of disease into the palate/upper alveolus and orbit from the nose and paranasal sinuses and also the patterns of disease presentations of Mucormycosis [MCM].

2. Materials and methods

This was a single center study undertaken for 3 months, in a tertiary referral public hospital during the peak of the epidemic of MCM in South India that commenced during the second wave of the COVID-19 pandemic. Clearance was obtained from the institutional ethics review board. Written informed consent was taken from all the patients. The study included patients of diabetes mellitus and COVID 19 history with and without orbital and or palatal involvement due to MCM of the nose.
and paranasal sinuses who had undergone surgical debridement for the same and also received Amphotericin B therapy.

The primary outcome was to identify the critical structures responsible for the involvement of the palate/alveolus, orbit or both [Regions]. The patterns of involvement of the various sites in the nose and the paranasal sinus [PNS] were also studied. This was a case-control study with 4 groups:

a. Case group A [A]: Nose, PNS and palate involved cases [stage 2]
b. Case group B [B]: Nose, PNS and orbit involved cases [stage 3]
c. Case group C [C]: Nose, PNS, palate and orbit involved cases [Stage 3] with CNS involvement [Stage 4]
d. Control group [D]: Nose, PNS or both involved cases [Stage 1]

Every consecutive eligible patient was included in the study. Adult patients in stages 1, 2, 3, 4 of MCM of head and neck with diabetes mellitus and post COVID-19 infection (Based on magnetic resonance imaging [MRI], Diagnostic nasal endoscopy [DNE], biopsy and clinical findings) [1,2]. Orbital involvement was confirmed by restriction of movement, loss or reduction of vision, chemosis, edema of eyelid, proptosis and redness of the eye. Palatal involvement was established by the presence of ulcer, swelling or loose tooth. Diabetes mellitus included precoid type 1, 2 or covid induced diabetes. Inoperable cases, chronic sinusitis without evidence of MCM or pre-existing diabetic retinopathy were excluded. A Scoring system to assess the bulk of disease for every patient was prepared according to the sites involved on the MRI and the net score was calculated [3]. The scoring pattern for the sites was as follows: middle/inferior turbinate, osteomeatal complex, nasal septum, cribriform plate, lateral wall of the maxillary cavity, infratemporal fossa, frontal sinus [Score 1], ethmoids, the floor of the nasal cavity, floor of the maxillary sinus, sphenoid sinus, roof of the maxillary sinus [score 2], pterygopalatine fossa, cavernous sinus [score 3]. The score of cases and controls was compared and analyzed.

2 * 2 contingency tables were prepared separately for every suspected risk factor and the Odds ratio was calculated. Chi-square test was used for the study of the association at 95% confidence intervals. The sensitivity and specificity of the MRI scores in identifying the disease of group A, B, C was calculated. Standard error was calculated [95% confidence intervals] and the ROC curve was obtained by plotting sensitivity against 1-specificity. Stata version 21 was used for statistical analysis.

3. Results

Two hundred and fourteen patients were studied in all that included 170 males and 44 females. The youngest patient was aged 25 years and the oldest 80 years. The mean age was 50.29 ± 11.47. The distribution of the patients according to the age class interval is shown in Fig. 1. The percentages of the patients in the individual groups and the admission discharge statistics are given in Table 1. The percentages of the patients in the individual groups and the admission discharge statistics are given in Table 1. The most common symptom and sign were craniofacial pain [Table 2] and nasal discharge [Table 3], respectively. The findings of the MRI done are given in Table 4 and the commonest site involved was the ethmoid sinus [Table 4]. The risk factor for each site was calculated by odds ratio and then the strength of the association with the palate and orbit [Table 5]. The MRI scores of the patients in the various groups is given in class intervals in Table 6. The area under the ROC curves of groups A, B, C is shown in Figs. 2, 3, 4, respectively. It was found that group C had the maximum area under ROC and hence the MRI scores were the most useful to identify the bulk of disease.

4. Discussion

In the past, several authors have studied a series of cases of MCM over the years [3-14]. Also, many cases of MCM have been reported recently (2021) across India and the rest of the world after the COVID-19

| Status of patient | A | B | C | D | Total |
|-------------------|---|---|---|---|-------|
| Undergoing treatment Palate | 28 | 51 | 36 | 25 | 140  [65.42%] |
| Discharged from hospital on request | 7 | 7 | 8 | 8 | 30 |
| Discharge against medical advice | 1 | 6 | 5 | 4 | 16 |
| Expired | 2 [5.26%] | 11 [14.66%] | 8 [14.03%] | 7 [15.90%] | 28 [13.08%] |
| Total | 38 [17.75%] | 75 [35.04%] | 57 [26.63%] | 44 [20.56%] | 214 |
pandemic [15–31]. However, none has evaluated the risk factors for palatal and orbital involvement against a control. To the best of our knowledge, this is the first paper to assess and report the same. Just as the course of COVID-19 was unpredictable and could become serious in some, so was MCM in this study. Given the high morbidity and mortality of the disease, it is essential to identify the sites in and around the nose and the paranasal sinuses that get involved early and play a lead role in the further extension of the disease to vital organs. There were no apparent reasons or causes for the spread into the palate, orbit or the central nervous system in a few of them. The involvement of these regions additionally required the services of a maxillofacial surgeon, a prosthodontist, an oculoplastic surgeon and a neurosurgeon in our setup. Hence the number of surgeries that the patient had to undergo would increase, thereby increasing the duration of surgery and also the number of times the patient was subjected to general anesthesia.

Diagnosis is confirmed through biopsy and histological analysis of the affected tissues. On microscopy, broad-based ribbon-like non-septate hyphae with irregular right-angled branching are the key diagnostic microscopic features [32]. CT and MRI scans may suggest invasive MCM but they may often be nondiagnostic [11]. If angio-invasion is present, bone erosion may be absent even in the presence of progressive disease. Overall, CT and MRI may be most helpful in assisting surgical planning for, rather than the diagnosis of rhinocerebral MCM [11].

Periorbital cellulitis, extraocular muscle paresis, proptosis and chemosis frequently develop due to disease extension into orbit or cavernous

Table 2
Symptoms in the 4 groups.

| Symptoms                  | A     | B     | C     | D     | Total |
|---------------------------|-------|-------|-------|-------|-------|
| Nasal obstruction         | 15    | 23    | 20    | 21    | 79    (36.91%) |
| Nasal discharge           | 13    | 14    | 12    | 11    | 59    (23.36%) |
| Craniofacial pain         | 27    | 54    | 36    | 27    | 144   (67.28%) |
| Blurred vision            | 0     | 22    | 11    | 6     | 39    (18.22%) |
| Eye swelling              | 7     | 55    | 41    | 5     | 108   (50.46%) |
| Fever                     | 2     | 9     | 4     | 3     | 18    (8.41%)  |
| Loose tooth/toothache     | 23    | 16    | 23    | 7     | 69    (32.34%) |
| Disorientation             | 0     | 1     | 2     | 0     | 3     (1.40%)  |
| Vomiting                  | 0     | 1     | 0     | 0     | 1     (0.46%)  |

Table 3
Signs in the 4 groups.

| Signs                        | A     | B     | C     | D     | Total |
|------------------------------|-------|-------|-------|-------|-------|
| Nasal discharge              | 21    | 52    | 33    | 28    | 134   (62.61%) |
| Nasal eschar/slough          | 15    | 30    | 36    | 22    | 103   (48.13%) |
| Eyelid edema                 | 3     | 57    | 37    | 4     | 101   (47.19%) |
| Eye congestion               | 1     | 27    | 23    | 0     | 51    (23.83%) |
| Diminished vision            | 0     | 26    | 15    | 0     | 41    (19.15%) |
| Restricted movements of eyeball | 0    | 29    | 21    | 0     | 50    (23.36%) |
| Proptosis                    | 0     | 21    | 15    | 0     | 36    (16.82%) |
| Palatal ulcer                | 30    | 0     | 41    | 0     | 71    (33.17%) |
| Loose or missing teeth       | 9     | 2     | 3     | 0     | 14    (6.54%)  |
| Altered sensorium            | 0     | 0     | 6     | 0     | 6     (2.80%)  |

Table 4
MRI findings suggesting the involvement of various sites in the craniofacial region.

| MRI findings of involvement [sites] | A     | B     | C     | D     | Total |
|-------------------------------------|-------|-------|-------|-------|-------|
| Middle turbinate                    | 6     | 20    | 12    | 14    | 52    (24.29%) |
| Inferior turbinate                  | 7     | 17    | 15    | 10    | 42    (19.62%) |
| Septum                              | 2     | 0     | 4     | 0     | 6     (2.80%)  |
| Lateral wall of maxillary sinus     | 18    | 40    | 26    | 22    | 106   (49.53%) |
| Roof of maxillary sinus             | 31    | 48    | 58    | 21    | 158   (73.83%) |
| Floor of maxillary sinus            | 33    | 48    | 32    | 25    | 138   (64.48%) |
| Floor of nasal cavity               | 3     | 5     | 3     | 1     | 12    (5.56%)  |
| Ethmoid sinus                       | 28    | 66    | 48    | 34    | 176   (82.24%) |
| Sphenoid sinus                      | 22    | 56    | 42    | 21    | 141   (65.88%) |
| Frontal sinus                       | 16    | 40    | 31    | 21    | 108   (50.46%) |
| Pterygopalatine fossa               | 4     | 7     | 8     | 3     | 22    (10.26%) |
| Infratemporal fossa                 | 8     | 24    | 12    | 5     | 49    (22.89%) |
| Cavernous sinus                     | 0     | 3     | 4     | 0     | 7     (3.27%)  |

Table 5
The odds ratio and the strength of association found between the sites of the craniofacial region and the palate, orbit.

| Site involved                  | Palate | Palate | Orbit | Orbit |
|--------------------------------|--------|--------|-------|-------|
|                                | Odds ratio | p-Value | Odds ratio | p-Value |
| Lateral wall of nasal cavity   | 0.39   | 0.001  | 1.63  | 0.09  |
| Floor of the maxillary sinus   | 1.3    | 0.28   | 0.63  | 0.13  |
| Roof of the maxillary sinus    | 10.74  | <0.001 | 2.35  | 0.007 |
| Lateral wall of maxillary sinus| 0.79   | 0.41   | 1.05  | 0.86  |
| Floor of nasal cavity/septum   | 2.72   | 0.05   | 1.26  | 0.67  |
| Ethmoid sinus                  | 0.76   | 0.45   | 2.04  | 0.05  |
| Sphenoid sinus                 | 1.12   | 0.69   | 2.61  | 0.001 |
| Frontal sinus                  | 0.93   | 0.80   | 1.41  | 0.22  |
| Pterygopalatine fossa          | 1.57   | 0.32   | 1.37  | 0.50  |
| Infratemporal fossa            | 0.82   | 0.57   | 1.99  | 0.05  |
| Cavernous sinus                | 1.7    | 0.52   | 9.86  | 0.02  |

Table 6
MRI scores of the patients in the 4 groups in class intervals.

| MRI score | A     | B     | C     | D     | Total |
|-----------|-------|-------|-------|-------|-------|
|           | Palate | Orbit | Both  | None  |
| 1–3       | 3      | 2     | 0     | 7     | 12    |
| 4–6       | 9      | 15    | 7     | 14    | 45    |
| 7–9       | 14     | 29    | 26    | 19    | 88    |
| 10–12     | 8      | 21    | 18    | 3     | 50    |
| 13–15     | 4      | 4     | 5     | 1     | 14    |
| 16–18     | 0      | 4     | 1     | 0     | 5     |
| Total cases| 38    | 75    | 57    | 44    | 214   |

Fig. 2. Area under the ROC curve in palatal involvement only.
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The disease in the roof of the maxillary sinus had a significant association and the highest risk to spread into the upper alveolus and the palate. The other sites with increased risk for palatal involvement were the floor of the nasal cavity and the pterygopalatine fossa. Similarly, the risk of involvement in orbit was highest when there was disease in the sphenoid sinus and the cavernous sinus. The other sites with significant association and high risk were the roof of the maxillary sinus, infra-temporal fossa and ethmoid sinus. Due attention should be given to the clearance of disease in these high-risk sites during debridement surgery to prevent common recurrences and thus reduce morbidity and mortality. The contiguous spread was not always the rule and skip lesions were possible due to perineural and transvascular spread. MRI scores were most helpful to identify the bulk of disease when both the palate and orbit were involved and least beneficial when the palate alone was involved.

Fig. 3. Area under the ROC curve in orbital involvement only.

Fig. 4. Area under the ROC curve in both palatal and orbital involvement.

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