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Case Report

Oncology Section

# Co-existence of Head and Neck Squamous Cell Carcinoma with Sinonasal Mucormycosis: Therapeutical Challenges

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## ABSTRACT

Pandemic was new experience for entire humanity. Medical fraternity was no exception. The cases of mucormycosis were on the rise during the second wave of the pandemic. Presented here are two cases which were combination of two diseases, one of which was squamous cell carcinoma of head and neck region (49-year-old male) and other one was sinonasal mucormycosis (56-year-old male). Both patients were diabetics and had history of Coronavirus Disease-2019 (COVID-19) infection in past. Our literature search doesn't reveal any previously reported cases of this rare combination. There were certain challenges in management. Both diseases were lethal and treatment of one cannot be prioritised over other. Challenges in managing those cases were, reconstruction planning, perioperative management and postsurgery adjuvant therapy. In absence of previous experience to treat this combination or any literature available new treatment protocol were formulated. Cases were discussed in multidisciplinary team meetings and treatment plans were formulated. Mucormycosis and oral squamous cell carcinoma both were operated and reconstructed in same sitting. In one patient revision endoscopic debridement had to be done. Amphotericin B was started once diagnosis was confirmed. Patients were followed-up on weekly basis during first month and imaging was done every 15 days. Both patients had satisfactory recovery without any sign of progression of mucormycosis. Adjuvant radiation was given in both cases at appropriate time. At follow-up both patients were free from disease for six months. From these unique experiences it can be recommended that combination of sinonasal mucormycosis and squamous cell carcinoma of head and neck is very rare. Both diseases can be treated simultaneously. excision and reconstruction can be done in single sitting. There is no need to delay or avoid adjuvant radiation. Multidisciplinary team approach is the key for treatment.

**Keywords:** Amphotericin B, Oral squamous cell carcinoma, Reconstruction planning

## CASE REPORT

### Case 1

A 49-year-old male patient presented to Department of Head and Neck Surgery with complaints of swelling at the left angle of the mandible for the last one month. His swelling was progressively increasing in size and was absolutely painless. He was chronic tobacco chewer. Diabetes Mellitus was diagnosed three months back and the patient was on antidiabetic medication. He also had history of COVID-19 infection three months back. Family history was insignificant. On examination, there was a swelling at level Ib on the left side of neck. Swelling was 4×4 centimetres in size. It was solid, hard with irregular edges, and fixed to underlying muscles. Skin over swelling was normal. Nothing abnormal was found in oral cavity.

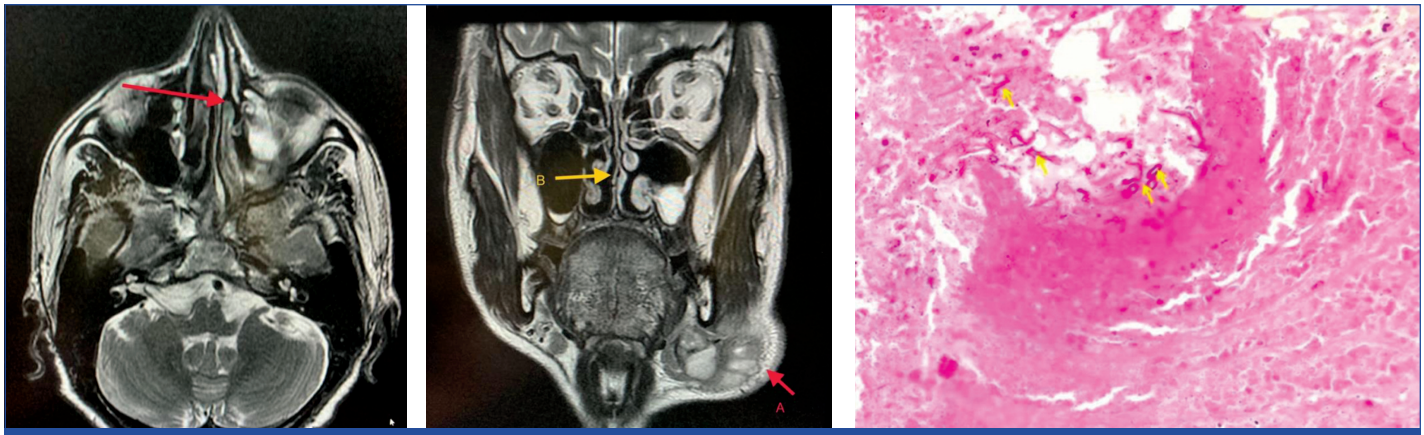
The patient underwent Positron Emission Tomography and Computed Tomography (PET-CT) scan which was suggestive of Fluorodeoxyglucose (FDG) avid mass at left level Ib, level II, and level III. The mass was adherent to tail of parotid gland, sternocleidomastoid muscle, and submandibular gland. There was inflammatory mucosal thickening in left maxillary sinus with an unexplained defect in medial wall of left maxillary sinus and non FDG avid fullness in left pterygopalatine fossa [Table/Fig-1,2]. Provisional diagnosis of squamous cell carcinoma of nasal cavity with cervical node metastasis was made. Differential diagnosis included co-existing inverted papilloma or sinonasal mucormycosis with separate cervical pathology like metastatic neck disease, tubercular lymphadenitis, lymphoma.

His Fine Needle Aspiration Cytology (FNAC) from left side of neck showed few clusters and singly dissociated atypical squamous cells and hyperchromatic nuclei suggesting keratinising squamous cell carcinoma metastatic type.

Treatment plan was to do superficial parotidectomy with left extended radical neck dissection for metastatic squamous cell carcinoma. Multiple samples were to be taken for frozen section and direct microscopy from suspected areas of left nasal cavity. If the microscopy suggested malignant then maxillectomy would be done. If mucormycosis was positive then endoscopic nasal debridement, if inverted papilloma then medial maxillectomy would be done.

The patient underwent left superficial parotidectomy with left extended radical neck dissection. Multiple endoscopic biopsies were taken from medial wall of maxillary sinus, maxillary sinus mucosa, and pterygopalatine fossa. Light microscopic examination of tissue from medial wall of left maxillary sinus was reported as "aseptate fungus" which was suggestive of mucormycosis. Tissue from pterygopalatine fossa and mucosa from maxillary sinus were reported negative. Endoscopic nasal debridement including medial maxillectomy, pterygopalatine fossa clearance anterior and posterior ethamoidectomy was done to complete the procedure. Reconstruction of neck was done with pectoralis major myocutaneous flap. Separate instruments were used for both procedures. During postoperative period nasal saline nasal wash was given every two hourly.

On postoperative day two histopathology [Table/Fig-3] and culture both confirmed the invasive mucormycosis infection. Patient was started with liposomal Amphotericin B from the second day onwards and was discharged after five postoperative days in stable condition to another multispecialty hospital for further antifungal treatment. He was followed-up clinically every week for one month and monthly thereafter. Imaging was done every 15 days for 45 days then on sos basis later. His final histopathology was suggestive of sinonasal mucormycosis with metastatic moderately differentiated squamous




**[Table/Fig-1]:** Axial view of contrast enhanced Magnetic Resonance Imaging (MRI) study with erosion of medial wall of left maxillary sinus. Represented by red (arrow).
**[Table/Fig-2]:** Coronal section of MRI scan: yellow arrow representing medial maxillary wall defect. Red arrow representing neck mass.
**[Table/Fig-3]:** Maxillary sinus content shows area of necrosis with broad non septate fungal hyphae (arrow) (H&E X400). (Images from left to right)

cell carcinoma [Table/Fig-4] with extra nodal extension T0N3B. Later clinical followed-up was done on monthly basis. He received 30 fractions and 60 grays of radiation. Chemotherapy was not given to avoid the combined side-effects of amphotericin B and chemotherapy. After adjuvant treatment patient was followed-up on monthly basis. Imaging was done after six months which was reported normal [Table/Fig-5,6].

## Case 2

A 56-year-old male patient presented at Department of Head and Neck Surgery with complaint of non healing ulcer in oral cavity for three months. The patient gave history of pain at right infraorbital region for two days. Ulcer was progressively increasing in size and was associated with trismus. The patient gave history of COVID-19 infection two months back. Diabetes mellitus and hypertension were two associated co-morbidities for last 6 and 7 years, respectively and was on medication for both. He had habit of tobacco chewing for last 25 years. Family history was not significant. He was diagnosed as moderately differentiated squamous cell carcinoma right buccal mucosa on the basis of the biopsy done two months back. Two cycles of neoadjuvant chemotherapy was given elsewhere (carboplatin, 5 flurouracil, paclitaxal).

On examination there was a proliferative lesion at right buccal mucosa which was involving skin of cheek with palpable IB node. Right infra orbital region was tender. Blackish brown necrotic material in right nasal cavity at inferior turbinate was noticed on diagnostic nasal endoscopy. Nasal tissue was sampled and sent for histopathological examination, direct microscopy and fungal culture.

He underwent contrast enhanced MRI scan with gadolinium contrast which was reported 52×40×41 millimetres (mms) lesion at right buccal mucosa, lower gingivo-buccal sulcus (GBS) with erosion of mandible. There were multiple enlarged right IB and level II nodes. 34×15×13 mms irregular non enhancing area was seen involving right ethmoid sinus, nasal septum, and inferior turbinate [Table/Fig-7].

Provisional diagnosis of sinonasal mucormycosis with squamous cell carcinoma righ buccal mucosa with metastatic neck disease was given. Differential diagnosis included inverted papilloma, angiofibroma, squamous cell carcinoma and rhinosporidiosis of nasal cavity with squamous cell carcinoma of the right buccal mucosa with metastatic neck disease.

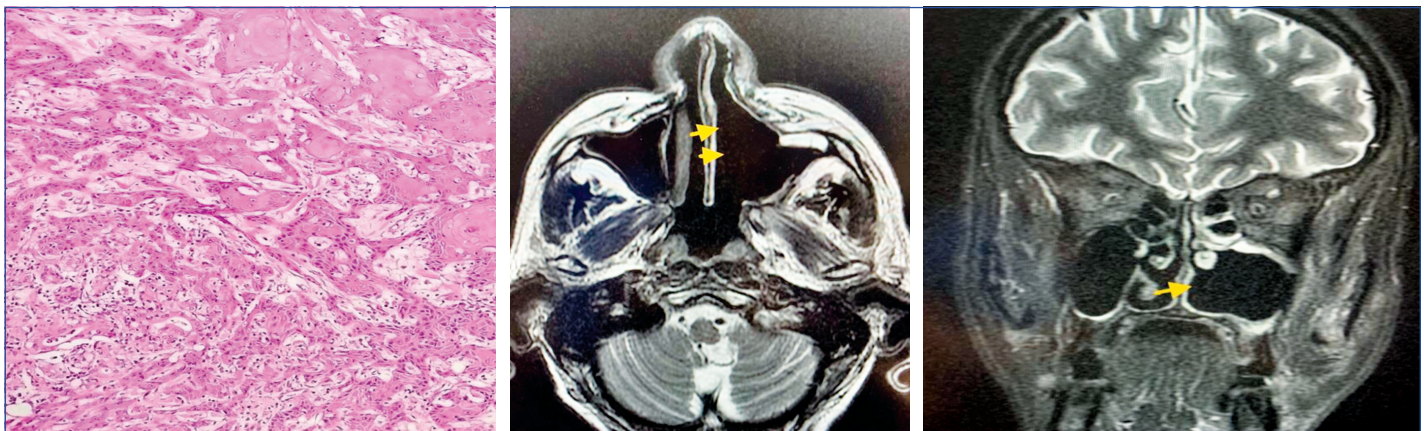
Direct microscopy and histopathology both confirmed presence of aseptate fungus which was suggestive of mucormycosis [Table/Fig-8].

Treatment plan was surgery followed by medical management with amphotericin B with appropriate adjuvant treatment.

He underwent right composite resection (full thickness right buccal mucosa, right segmental mandibulectomy with limited Infra Temporal Fossa (ITF) clearance with right supra omohyoid neck dissection with sinonasal debridement and medial maxillectomy and antero-lateral thigh flap reconstruction under general anaesthesia. Liberal saline wash was given to avoid cross contamination and separate instruments were used for both procedures.

On the next day he was started with liposomal amphotericin B under supervision of a physician. During postoperative period nasal wash was given every two hourly.

On postoperative day two he complained of severe right infra orbital pain which was not responsive to analgesics. On third postoperative day revision endoscopic debridement was performed. His pain subsided after the second surgery. His postoperative period of

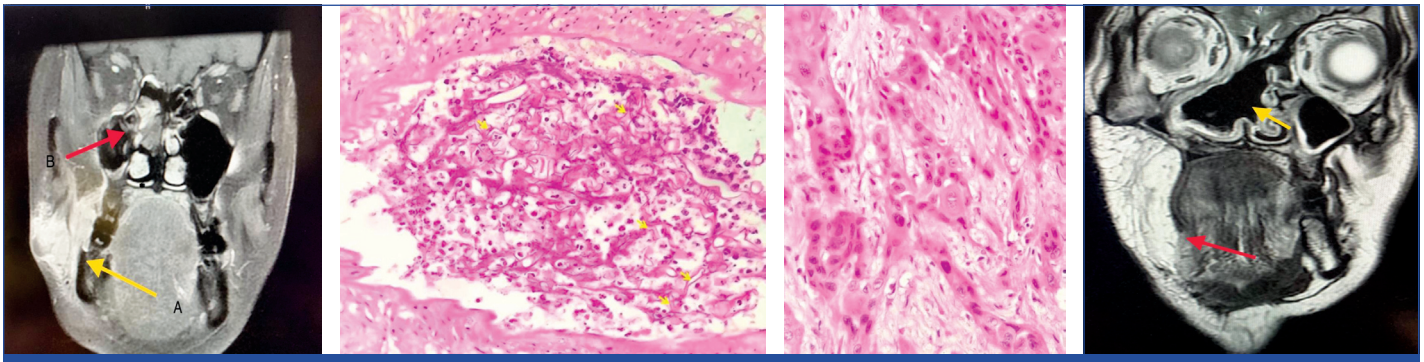


**[Table/Fig-4]:** Nodal mass at left level I,II,III shows nests of metastatic keratinising moderately differentiated squamous cell carcinoma (H&EX400). **[Table/Fig-5]:** Followed-up contrast enhanced MR imaging (axial section) showing post left medial maxillectomy status with no evidence of active mucormycosis infection (Yellow arrow- medial maxillectomy).
**[Table/Fig-6]:** Follow-up contrast enhanced MR imaging (coronal) showing post medial maxillectomy status with no evidence of mucormycosis. Yellow arrow: medial maxillectomy. (Images from left to right)

seven days was uneventful and was transferred to the Government medical hospital for liposomal amphotericin B later. He was kept on weekly follow-up. Contrast enhanced MRI was advised every 15 days for three times. His postoperative follow-ups were normal and MR studies remained static. Final histopathology was reported as moderately differentiated squamous cell carcinoma right buccal mucosa [Table/Fig-9] with sinonasal mucormycosis. Multiple positive nodes at Ib and level 2 (T4aN3b AJCC).

This patient was also a candidate for chemoradiation. Joint discussion with a medical and radiation oncologist was done. To avoid combined side-effects of amphotericin B and chemotherapy finally he received 60 grays and 30 fractions of Intensity Modulated Radiation Therapy (IMRT) instead of concurrent chemoradiation.

He was being followed clinically on monthly basis and imaging was done after six months which was reported normal postsurgical status without any active disease [Table/Fig-10].




**[Table/Fig-7]:** Coronal section of contrast enhanced MRI scan, with malignant lesion at right buccal mucosa (yellow arrow) and non enhancing area at right ethmoid sinus at right nose (red arrow). **[Table/Fig-8]:** Nasal mucosa tissue shows broad non septate fungal hyphae (arrows) (H&EX400). **[Table/Fig-9]:** Right buccal mucosa mass shows keratinising moderately differentiated squamous cell carcinoma (H&EX400). **[Table/Fig-10]:** Follow-up contrast enhanced MR imaging (coronal) showing post medial maxillectomy status with no evidence of mucormycosis. Yellow arrow medial maxillectomy. Red arrow postoperative reconstruction for squamous cell carcinoma. (Images from left to right)

## DISCUSSION

Squamous cell carcinoma of the oral cavity is very common in India, especially in the central or western part of the country [1]. Surgery at an early stage of disease is one of the prime factors which determines prognosis [2]. So it is recommended that surgery should be done as soon as possible. On the other hand, mucormycosis is a life-threatening condition characterised by rapid progression and high mortality from 50-100% [3]. Mucormycosis is caused by various fungi from order mucorales. Sign and symptoms of sinonasal mucormycosis includes nasal discharge/crusting, facial pain, proptosis and loss of vision [4]. Mucormycosis occurs in two forms: invasive which is fulminant and the other one non invasive. Patients with leukaemia, neutropenia, diabetes mellitus, acute renal failure, antineoplastic medication and immunocompromised states are more at risk [5].

Literature search didn't yield any previous papers or case reports where both diseases were found in one patient at the same time. Sinonasal mucormycosis and squamous cell carcinoma are individually rare diseases. Combination of these two diseases is rarer. Countrywide vaccination, infrastructure development, understanding of pathogenesis of development of mucormycosis has enabled us to prevent future COVID-19 outbreaks and mucormycosis. Because of the same reason we may not find this rare combination in future.

The challenges were:

- No guidelines available to manage simultaneous occurrence of sinonasal mucormycosis and oral squamous cell carcinoma.
- Should treatment of one is to be prioritised over other or simultaneous treatment possible?
- Can mucormycosis infection cause destruction of reconstructive surgery? Should we postpone the reconstruction to the second stage?
- What should be the follow-up protocol?
- Can postoperative state flare up the mucormycosis?
- What is the appropriate time to start or stop amphotericin B?
- Can adjuvant treatment simultaneously be administered with amphotericin B. Or should it be delayed ?
- Should we limit the dose of adjuvant treatment?

### Difficult Diagnosis

Diagnosis of mucormycosis with minimal symptoms can be missed. Even symptomatic mucormycosis can be missed as symptoms can be attributed to cancer. Usually contrast enhanced MRI scan with gadolinium contrast is adequate imaging for both oral cancer and sinonasal mucormycosis [6]. In one case the diagnostic credit must be given to the radiologist who pointed out unexplained bony erosion in nasal cavity. For oral squamous cell carcinoma biopsy is gold standard and prerequisite for commencement of treatment [7]. Similarly biopsy/direct microscopy or fungal culture is required to start amphotericin B treatment [8]. Once radiologist suspected, samples were taken to prove the synchronous occurrence of squamous cell carcinoma and sinonasal mucormycosis.

### Counselling and Consent for Treatment

In the light of the present knowledge, we can assume presence of mucormycosis with squamous cell carcinoma may increase the chances of failure of flap [9], requirement of recurrent debridements and prolonged hospital stay. Proper counselling was paramount. Both cases were counselled at every step which resulted in satisfied patient and relatives at the end of treatment.

### Which One is to be Treated First?

Neither published literature nor guidelines are available for synchronous occurrence of mucormycosis and oral squamous cell carcinoma. Both diseases were lethal as well as progressive. Availability of endoscopic skull base surgeon, head and neck surgeon, reconstructive team, necessary infrastructure and multidisciplinary team made it easy to plan both surgeries in one sitting.

### Extra Surgical Care

Squamous cell carcinoma was excised via intra-oral/cervical approach while mucormycosis debridement was done endoscopically via transnasal approach. Since surgery resulted in common oro-nasal cavity in both cases, liberal saline wash was given to avoid contamination. Instruments of both the cases were kept separate. Operating surgeon descrubbed and rescrubbed again while switching from one procedure to another. Frequency of oral nasal wash was raised upto 2 hourly in day and every 4 hrs at night till completion of treatment.

### Reconstruction should be Delayed or Done Simultaneously?

In one case microvascular reconstruction was done while in the other Pectoralis Major Myocutaneous (PMMC) flap was done. Both flaps survived. Diabetes was a risk factor for progression of mucormycosis. Invasive mucormycosis has a tendency to spread in surrounding areas. Diabetes Mellitus was also an independent risk factor of vascular failure in microvascular reconstruction [10]. There might be increased total risk of flap compromise in presence of both diseases [9,10]. To manage diabetes mellitus strict blood sugar monitoring was done.

From this experience it can be recommended that reconstruction can be done in same sitting. Revision debridement was done in one patient as he developed pain in the right periorbital area. Pain subsided after revision surgery. Both patients were discharged on the fifth postoperative day. Both patients were shifted to another multispeciality unit for further medical management.

### Follow-up Protocol

Both patients were kept on regular weekly follow-up as usually done in routine patients with oral squamous cell carcinoma. Initially, MRI scan every 15 days is recommended. After three consecutive MRI studies remained static it was decided to get imaging at the time of appearance of new symptoms.

### Can Adjuvant Treatment be Administered with Amphotericin B?

As per final histopathology report, both patients should be considered for chemoradiation. As there were no guidelines these cases were discussed with radiation and medical oncologists. In the view of the need of amphotericin B treatment for mucormycosis and there was risk of increased nephrotoxicity in simultaneous administration of amphotericin B and chemotherapy [11] it was decided to avoid chemotherapy.

Liposomal amphotericin B was started from 2nd postoperative day and continued with adjuvant chemotherapy. At the time of completion of treatment both patients were asymptomatic. Till follow-up both patients had completed disease free six months.

## CONCLUSION(S)

Synchronous occurrence of both mucormycosis is rare and never reported. There are no guidelines available. From this rare experience it can be recommended that both diseases can be treated simultaneously. With careful and vigilant approach reconstruction can be done in same sitting. There is no need to compromise in management of either squamous cell carcinoma or mucormycosis. No need to delay or avoid adjuvant radiation. Multidisciplinary institutional management is a key to success.

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