Biological Forum – An International Journal **15(5a): 603-607(2023)**

ISSN No. (Print): 0975-1130
ISSN No. (Online): 2249-3239

Rhino-maxillary Mucormycosis with Associated Actinomycosis: Fungal and Bacterial Collusion

Godge Pournima[1], Shroff Jashika[2], S.M. Meghana[3*], Kulkarni Sandip[4] and Shah Rohit[5]

[1]MDS, Professor and HOD, Department of Oral Pathology and Microbiology, Terna Dental College, Navi Mumbai (Maharashtra), India.
[2]MDS, Lecturer, Department of Oral Pathology and Microbiology, Terna Dental College, Navi Mumbai, (Maharashtra), India.
[3]Ph.D. Research Scholar, DY Patil University School of Dentistry, Nerul, Navi Mumbai. MDS, Associate Professor, Department of Oral Pathology and Microbiology, Terna Dental College, Navi Mumbai, (Maharashtra), India.
[4]MDS, Associate Professor, Department of Oral Pathology and Microbiology Terna Dental College, Navi Mumbai (Maharashtra), India.
[5]Ph.D. Research Scholar, Karnavati University, Gandhinagar (Gujarat), India.

Corresponding author: S.M. Meghana)*
(Received: 04 April 2023; Revised: 29 April 2023; Accepted: 03 May 2023; Published: 15 May 2023)
(Published by Research Trend)

ABSTRACT: Mucormycosis, an acute angioinvasive fatal disease caused by filamentous fungi of order mucorales has emerged as an important fungal infection in immunocompromised patients with a mortality of 10% to as high as 100%. One of the aggressive variants of the disease is rhinocerebralmucormycosis, which is further subdivided into rhinomaxillary and rhino-oculocerebral forms of the infection. Concomitant fungal and bacterial infection of the maxillofacial region along with mucormycosis although uncommon, due to rich vascularity of this specific region, may present with widespread jaw bone necrosis and poses a diagnostic challenge for an oral physician. Here, we present an unusual case of rhinomaxillary form of mucormycosis developed post extraction, associated with granulomatous suppurative actinomycosis, in a 50 year-old diabetic male.

Keywords: Mucorales, ray fungus, concomitant infection, immunocompromised patient, Maxilla, Diabetes Mellitus.

INTRODUCTION

Mucormycosis, originally known as zygomycosis, or phycomycosis is a fulminant opportunistic infection caused by fungi belonging to the Mucorales order with Rhizopusoryzae (Rhizopusarrhizus) being the chief offender (Marx *et al.*, 2003). First described and termed as mycosis mucorina by German pathologist "Paultauf" (1885), in a 52 year old man (Prabhu *et al.*, 2004). It is the third most invasive mycotic infection after candidiasis and aspergillosis, and accounts for 8.3–13% of all fungal infections (Garlapati *et al.*, 2014) Based on clinical presentation and the involvement of a particular anatomic site, mucormycosis can be divided into at least six clinical categories: (a) rhinocerebral, (b) pulmonary, (c) cutaneous, (d) gastrointestinal, (e) disseminated, and (f) miscellaneous(O'Neill *et al.*, 2006).Ubiquitous in nature, the fungus is normally found in soil, manure, bread mould, decaying fruits, and nasal mucosa (Jagdish *et al.*, 2012). Immunocompromised individuals with an underlying disease such as leukemia, lymphoma, uremia, liver cirrhosis, malnutrition, organ transplants, and cancer chemotherapy are at a high risk (Jagdish *et al.*, 2012). Patients with diabetes mellitus and ketoacidosis are affected in almost 40-50% cases (Tierney *et al.*, 1995). In recent Covid 19 pandemic, immunocompromised patients have shown higher probability of suffering from invasive mycosis (Song *et al.*, 2020). Oral mucormycotic infection is usually caused by inhalation of spores or direct contamination of open oral wound. However, those occurring subsequent to tooth extraction are infrequent (Kim *et al.*, 2001).

Concomitant opportunistic infections with mucormycosis, most common being aspergillosis, are rare within the maxillofacial region owing to its rich oxygen supply (Kim *et al.*, 2001; Wali *et al.*, 2012). One such gram positive commensals of the oral region, previously described as a fungus due to its filamentous morphology, from the Actinomycetaceae family (genus Actinomyces), and the cause of actinomycosis, can occur in combination with mucormycosis. Although 30 species have been described, amongst these non-spore forming opportunists, actinomycesisraelliare most prevalent species in human infections followed by the less frequent actinomycesviscoses and actinomyces meyeri (Veenakumari *et al.*, 2017).

Cervicofacial actinomycosis of maxilla is unusual when compared to mandible which involves almost 50% cases. As patients with advanced disease are rare in the antibiotic era, actinomycosis has become a diagnostic challenge (Wali *et al.,* 2012; Veenakumari *et al.*, 2017). Here we present a rare case report of concomitant Rhinocerebral Mucormycosis and Actinomycosis of the maxilla causing extensive destruction and necrosis in a 50-year male with uncontrolled diabetes.

CASE REPORT

A 50-year-old male patient reported to the outpatient department of Terna Dental College with a chief complaint of pain and discharge in the upper right back region of the jaw, 2 months post-extraction which was relieved by intake of NSAIDs. Past medical history revealed uncontrolled type 2 diabetes since 1 year and patient was under medication for the same. There was also a history of associated hepatosplenomegaly, right simple renal cortical cyst (since 1 month) and hypertension. On general examination the patient was cooperative and conscious with no signs of anemia or jaundice.

On extraoral examination (Fig. 1), there was a mild diffuse swelling over the right middle third of the face with normal overlying skin. On palpation, there was local rise in the temperature when compared with the opposite side. Swelling was firm in consistency, non-fluctuant, non- reducible, non-pulsatile, non-compressible but tender. There was a history of intermittent fever since a few days. No paresthesia or lymphadenopathy was noted.

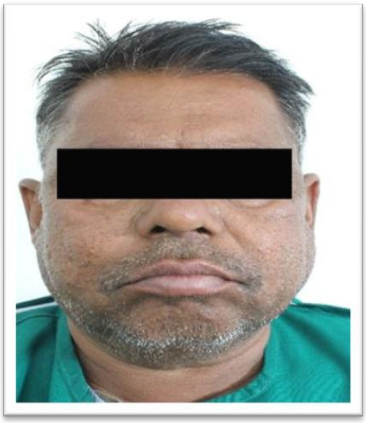

Fig. 1. Diffuse swelling over the right middle third of the face with normal overlying skin.

Intraoral oral examination showed (Fig. 2) an area of dehiscence over the right maxillary alveolus with an oroantral fistula and loss of mucoperiosteum over the maxillary alveolar process, involving the 14 and 15 regions. The adjacent mucosa on the buccal aspect was swollen and inflamed. On palpation, oroantral communication was present and the affected submucosal area was soft in texture with mild tenderness. The right maxillary premolars were missing confirming the history of previous extraction. There was necrosis which was associated with a purulent discharge. Based on the history and clinical findings, provisional diagnosis of chronic inflammatory/infective lesion was arrived at. The differential diagnoses of osteomyelitis and malignancy were considered. The patient was advised Orthopantomogram (OPG), which showed a destructive lesion involving apical region of 14,15 with empty extraction sockets.

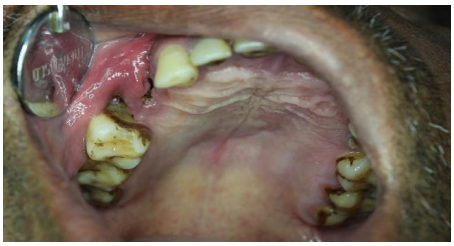

Fig. 2. Oroantral fistula over the maxillary alveolar process involving 14 and 15 regions.

Haematological values were found to be normal except for neutrophilic leucocytosis, elevated erythrocyte sedimentation rate and HbA1C (8.3%). Fasting blood sugar measured 112mg/dl. Also, the patient tested negative for COVID-19 infection.

CT scan of face and neck (plain and contrast) (Fig. 3) revealed ill-defined, destructive, infiltrative and expansile bone lesion involving maxillary alveolar arch and adjacent hard palate on right side with irregular heterogenous contour of alveolar ridge. The lesion also involved floor of nasal cavity, inferior wall of right maxillary sinus and lower part of bony nasal septum. There was sclerosis and thickening of the walls of right maxillary sinus, right zygomatic arch, both the pterygoid plates on the right side and surrounding hard palate. Features were suggestive of infiltrative lesion like osteomyelitis.

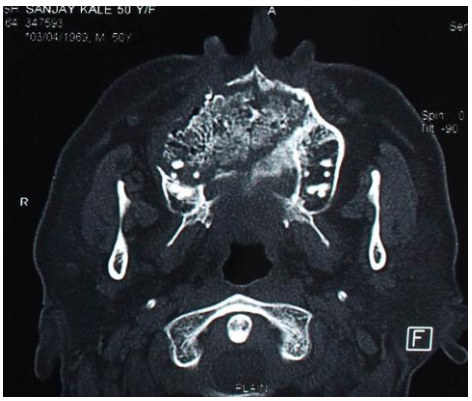

Fig. 3. CBCT scan revealing ill defined, destructive, infiltrative and expansile bony lesion.

Swabs were taken and cytological smears along with bacterial culture were prepared and stained. Gram staining demonstrated moderate amounts of pus cells, many filamentous long and short slender gram positive bacilli with occasional cocci. Preoperative fungal culture on blood agar, MacConkey agar and Sabouraud's agar confirmed the presence of mucor and actinomycotic growth.

Incisional biopsy was performed on the left maxillary alveolar ridge. Sections prepared and stained with H&E showed areas of necrotic bone devoid of any cellular activity. Presence of numerous fungal hyphae and

bacterial conglomerates resembling actinomycotic colonies with sunburst appearance were noted (Fig. 4). These colonies were surrounded by blood vessels and moderate to dense amounts of chronic inflammatory infiltrate. Fungal hyphae were broad, non-septate and branching at right angles in a ribbon like pattern, suggestive of Mucormycosis (Fig. 5). Antibiotic therapy was instituted post culture and sensitivity test performed on the discharge collected from the infection site. The patient was advised chlorehexidine mouthwash 3 times a day after meals for 15 days. Antibacterial therapy consisting of amoxicillin 500 mg, potassium clavulanate 125 mg, twice a day and liposomal Amphotericin B (0.5-5mg/kg for 3 weeks) injections were instituted.

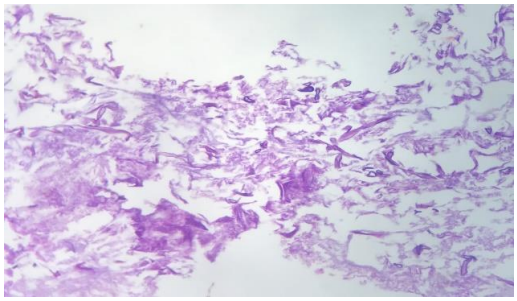

Fig. 4. Bacterial conglomerates resembling actinomycotic colonies (H&E, 10X).

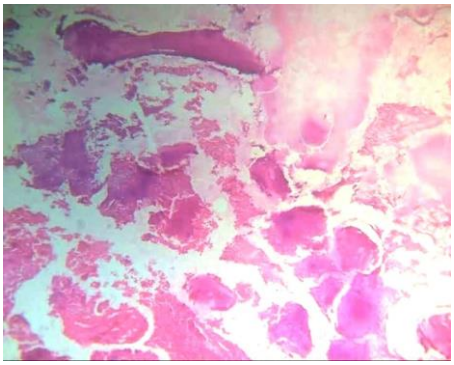

Fig. 5. Areas of necrotic bone with numerous fungal hyphae (H&E, 10X).

Surgical debridement of the affected bone and soft tissue was planned under general anaesthetia with primary closure. Prior to the intervention, routine biochemical, serological, and hematological examinations were done. Surgical debridement was performed and postoperative antifungal therapy was given.

Findings on excisional biopsy were suggestive of Mucormycosis with actinomycosis. Diagnosis was further confirmed with two special stains. Periodic Acid Schiff staining revealed PAS-positive hyphae stained in bright magenta red color (Fig. 6). Whereas Grocott's methenamine silver staining showed aseptate Mucorales hyphae and fungal spores along with actinomycotic colonies. Healing post-surgery as reviewed after 3 weeks was uneventful and patient was rehabilitated with acrylic palatal stent (Fig. 7).

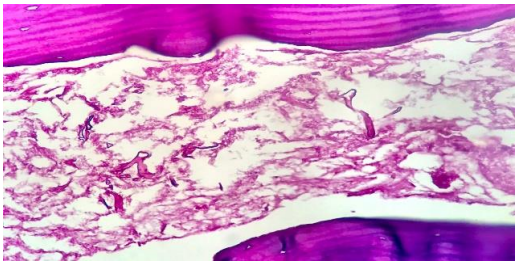

Fig. 6. Periodic Acid Schiff stain showing numerous non septate fungal hyphae (40X).

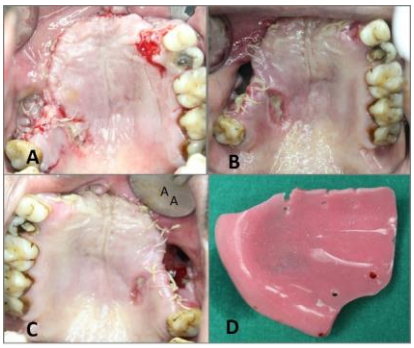

Fig. 7. Post-operative healing after: 1 week (A), 2 weeks (B), 3 weeks (C) and palatal stent (D).

DISCUSSION

The mucorymcosis is a rare opportunistic, life-threatening infection caused by saprophytic fungi belonging to mainly rhizopus (90%) or mucor genera and class phycomycetes. 11 genera and 27 species under Mucorales are known to be associated with human infections (Jeong *et al.*, 2019; Prakash *et al.*, 2019). The incidence of this infection is on a rise especially in India and China among patients with uncontrolled diabetes mellitus. The global mucormycosis case fatality rate is 46% (Prakash *et al.*, 2019). During the current pandemic of COVID-19, a myriad of manifestations and complications have emerged and are being reported with one of them being Mucormycosis. COVID-19 patients with trauma, diabetes mellitus, corticosteroid use, heamatologic malignancy, prolonged neutropenia, allo-haematopoietic stem cell transplant, solid organ transplant are more likely to develop Mucormycosis (Prakash *et al.*, 2019; Cornely *et al.*, 2019). Mucorales can gain entry to a susceptible host through inhalation, ingestion of contaminated food, or abraded skin. These routes result in rhino-orbito-cerebral, pulmonary, gastrointestinal, or cutaneous/wound infections. Rhino-cerebral mucormycois is the most common type affecting paranasal sinuses, maxilla, orbit and may extend to the brain in diabetic patients (Pilmis *et al.*, 2018).

Mucormycosis of the maxillofacial region uncommonly can coexist with other infections, with asperigillosis being the commonest (Chamilos *et al.*, 2008). Other such infections labelled as one of the most misdiagnosed disease, is actinomycosis which when coupled with muormycosis can rapidly spread through adjacent tissues causing extensive local destruction if not managed appropriately. A chronic granulomatous,

suppurative disease caused by Actinomyces Israeli, a ray fungus (from *Greek* actis: ray or beam, and mykes: fungus), it was first described by Von Langbeck in 1845 in humans. Waksman, later in 1960s showed that Actinomyces was a gram positive bacteria (Rani *et al.*, 2019). This filamentous, non-spore forming anaerobic or microaerophilic fastiduous bacteria belongs to the genus Actinobacteria. They are opportunistic pathogens and in combination with companion microbes can contribute to initiation and development of infections by inhibiting host defences or reduced oxygen tension. In 1938, Cope classified the disease into three types; 1) cervicofacial 2) abdominal 3) pulmonary. Cervicofacial disease is the most common type, characterised by a painless "Lumpy jaw" and the formation of multiple abscesses and sinus tracts discharging sulphur granules. Lymphadenopathy is uncommon in this disease. Cervicofacial actinomycosis involves mandible (50%) of cases, cheek (15%), chin (15%), and submaxillary ramus and angle (10%) (Veenakumari *et al.*, 2017; Urs *et al.*, 2019).

In the present case, the patient had a localised rhinomaxillary form of the disease affecting the floor of maxillary sinuses, which is a well-documented subdivision of rhino cerebral Mucormycosis without involvement of brain or orbit along with collateral actinomycosis of the maxilla.

Mucormycotic infections exhibit extensive angioinvasion with resultant vessel thrombosis and tissue necrosis which is attributed to the ability of the organism to hematogenously disseminate from the original site to target organs. Clinical evidence has demonstrated that both mononuclear and polymorphonuclear phagocytes of normal hosts kill mucorales by the generation of oxidative metabolites and the cationic peptides defensins. Hyperglycemia and ketoacidosis in diabetes impairs the ability of phagocytes and increases production of enzyme ketoreductase in mucormycotic patients making ketone bodies available for their nutrition (Afroz *et al.*, 2017). Chronic renal insufficiency is another such illness that predispose to mucor infections. The present case was of a known diabetic with underlying simple right renal cortical cyst and hepatosplenomegaly.

Collateral blood supply, porous nature and thin cortices of maxilla reduce the chance of osteomyelitis and necrosis in maxilla compared to the mandible (Gannepalli *et al.*, 2015). Underlying diabetes with thrombosis of internal maxillary artery or descending palatine artery would have consequentially resulted in necrosis of maxilla in the present case.

Along with Mucormycosis, asperigillosis, is one of the most common invasive fungal infections affecting immunocompromised individuals and should be considered in differential diagnosis. Definitive diagnosis of Mucormycosis is based on histopathological examination which shows extensive areas of tissue necrosis and the presence of numerous fungal aseptate hyphae with nondichotomous branching at right angle, whereas septate branching hyphae with branching at acute angles, smaller in width producing conidiospores is seen in aspergillosis (Rani *et al.*, 2019). Presence of non-septate hyphae with branching at obtuse angle which stained positive with periodic acid Schiff (PAS) stain, confirmed the diagnosis of Mucormycosis.

For actinomycosis the most appropriate clinical specimens are samples of tissue, pus or sulphur granules. Culturing actinomyces bacteria can be extremely difficult due to its anaerobic nature making Gram staining more sensitive than culture. Demonstration of Gram positive filamentous organisms and sulphur granules is strongly supportive of a diagnosis of actinomycosis (Urs *et al.*, 2019). Sulphur granules could not be demonstrated in our case which could be attributed to the transitory nature of the disease. However, bacterial conglomerates resembling actinomycotic colonies with sunburst appearance, admixed with blood vessels and chronic inflammatory cell infiltrate were noted.

Treatment modality includes control of the underlying risk factors, antifungal therapy, surgical debridement, supportive therapy, and surgical or prosthetic rehabilitation (Spellberg *et al.*, 2005).

Covid, diabetes milletus and mucormycosis:

There was an unusual surge in the number of rhino-orbital mucormycosis reported in patients suffering from COVID-19, particularly from India. An unholy trinity of diabetes, rampant use of corticosteroid in a background of COVID-19 appeared to increase mucormycosis (Singh *et al.*, 2021).

Globally, the prevalence of mucormycosis varied from 0.005 to 1.7 per million population, while its prevalence is nearly 80 times higher (0.14 per 1000) in India compared to developed countries, in a recent estimate of year 2019–2020 (Prakash *et al.*, 2019; Skiada *et al.*, 2020; Chander *et al.*, 2018) Not withstanding, India is already having second largest population with diabetes mellitus (DM) and was the diabetes capital of the world, until recently (IDF, 2019). Importantly, DM has been the most common risk factor linked with mucormycosis in India, although hematological malignancies and organ transplant takes the lead in Europe and the USA (Prakash *et al.*, 2019). Nevertheless, DM remains the leading risk factor associated with mucormycosis globally, with an overall mortality of 46% (Jeong *et al.*, 2019). Therefore, through this article, we wish to convey that efforts should be taken to maintain optimal blood sugar levels and only prudent, evidence-based use of corticosteroids in patients with COVID-19 is advised in order to ease the burden of developing fatal mucormycosis.

CONCLUSIONS

Simultaneous coexistence of two fatal diseases of cervicofacial region, mucormycosis and actinomycosis may be diagnostically challenging for dental surgeons due to unfamiliarity with its clinical presentation. Early and prompt recognition of such conditions which tend to spread rapidly is very crucial as they may mimic dental-related infections simulating a malignant disease. And frequently, they may be associated with underlying systemic conditions that may be quiescent. Finally, a multi-disciplinary team approach along with early

diagnosis, management of underlying medical condition accompanied by aggressive surgical intervention are the key to improving the outcome of such patients.

REFERENCES

Afroze, S. N., Korlepara, R., Rao, G. V., & Madala, J. (2017). Mucormycosis in a diabetic patient: a case report with an insight into its pathophysiology. *Contemporary clinical dentistry*, *8*(4), 662.

Chamilos, G., Lewis, R. E., & Kontoyiannis, D. P. (2008). Delaying amphotericin B–based frontline therapy significantly increases mortality among patients with hematologic malignancy who have zygomycosis. *Clinical Infectious Diseases*, *47*(4), 503-509.

Chander, J., Kaur, M., Singla, N., Punia, R. P. S., Singhal, S. K., Attri, A. K., ... & Guarro, J. (2018). Mucormycosis: battle with the deadly enemy over a five-year period in India. *Journal of fungi*, *4*(2), 46.

Cornely, O. A., Alastruey-Izquierdo, A., Arenz, D., Chen, S. C., Dannaoui, E., Hochhegger, B., ... & Chakrabarti, A. (2019). Global guideline for the diagnosis and management of mucormycosis: an initiative of the European Confederation of Medical Mycology in cooperation with the Mycoses Study Group Education and Research Consortium. *The Lancet infectious diseases*, *19*(12), e405-e421.

Garlapati, K., Chavva, S., Vaddeswarupu, R. M., & Surampudi, J. (2014). Fulminant mucormycosis involving paranasal sinuses: A rare case report. *Case reports in dentistry*, *2014*.

Gannepalli, A., Ayinampudi, B. K., Baghirath, P. V., & Reddy, G. V. (2015). Actinomycotic osteomyelitis of maxilla presenting as oroantral fistula: a rare case report. *Case Reports in Dentistry*, *2015*.

Song, G., Liang, G., & Liu, W. (2020). Fungal co-infections associated with global COVID-19 pandemic: a clinical and diagnostic perspective from China. *Mycopathologia*, *185*(4), 599-606.

Jagdish, C., Reetika, S., Pallavi, S., Jayanthi, S., Divya, P., & Balasubramanya, A. (2012). Mucormycosis of the paranasal sinus with gas forming maxillary osteomyelitis—a case report. *The Internet Journal of Microbiology*, *10*(1), 1-6.

Jeong, W., Keighley, C., Wolfe, R., Lee, W. L., Slavin, M. A., Kong, D. C. M., & Chen, S. A. (2019). The epidemiology and clinical manifestations of mucormycosis: a systematic review and meta-analysis of case reports. *Clinical microbiology and infection*, *25*(1), 26-34.

Kim, J., Fortson, J. K., & Cook, H. E. (2001). A fatal outcome from rhinocerebral mucormycosis after dental extractions: a case report. *Journal of oral and maxillofacial surgery*, *59*(6), 693-697.

Marx, R. E., & Stern, D. (2012). *Oral and maxillofacial pathology: a rationale for diagnosis and treatment* (pp. 667-720). Hanover Park: Quintessence Publishing Company.

O'Neill, B. M., Alessi, A. S., George, E. B., & Piro, J. (2006). Disseminated rhinocerebral mucormycosis: a case report and review of the literature. *Journal of oral and maxillofacial surgery*, *64*(2), 326-333.

Prabhu, R. M., & Patel, R. (2004). Mucormycosis and entomophthoramycosis: a review of the clinical manifestations, diagnosis and treatment. *Clinical Microbiology and Infection*, *10*, 31-47.

Prakash, H., & Chakrabarti, A. (2019). Global epidemiology of mucormycosis. *Journal of Fungi*, *5*(1), 26.

Pilmis, B., Alanio, A., Lortholary, O., & Lanternier, F. (2018). Recent advances in the understanding and management of mucormycosis. *F1000Research*, *7*.

Rani, S. U., Sivaranjani, Y., Kumar, M. P., & Rao, G. V. (2019). Rhinocerebral mucormycosis associated with actinomycosis in a diabetic patient: A rare presentation. *Journal of oral and maxillofacial pathology: JOMFP*, *23*(Suppl 1), 122.

Spellberg, B., Edwards Jr, J., & Ibrahim, A. (2005). Novel perspectives on mucormycosis: pathophysiology, presentation, and management. *Clinical microbiology reviews*, *18*(3), 556-569.

Skiada, A., Pavleas, I., & Drogari-Apiranthitou, M. (2020). Epidemiology and diagnosis of mucormycosis: an update. *Journal of fungi*, *6*(4), 265.

Singh, A. K., Singh, R., Joshi, S. R., & Misra, A. (2021). Mucormycosis in COVID-19: a systematic review of cases reported worldwide and in India. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews*, *15*(4), 102146.

Tierney, M. R., & Baker, A. S. (1995). Infections of the head and neck in diabetes mellitus. *Infectious disease clinics of North America*, *9*(1), 195-216.

Urs, A. B., Augustine, J., & Singh, S. (2019). Histopathological evaluation of a rare fulminant case of contemporaneous mucormycosis, aspergillosis and actinomycosis. *Journal of Oral and Maxillofacial Pathology: JOMFP*, *23*(1), 144.

Veenakumari, L., & Sridevi, C. (2017). Actinomycosis in histopathology-Review of literature. *International Archives of Integrated Medicine*, *4*(9), 195-206.

Wali, U., Balkhair, A., & Al-Mujaini, A. (2012). Cerebro-rhino orbital mucormycosis: an update. *Journal of infection and public health*, *5*(2), 116-126.

How to cite this article: Godge Pournima, Shroff Jashika, S.M. Meghana, Kulkarni Sandip and Shah Rohit (2023). Rhino-maxillary Mucormycosis with Associated Actinomycosis: Fungal and Bacterial Collusion. *Biological Forum – An International Journal*, *15*(5a): 603-607.