DOI: 10.7860/JCDR/2023/61240.17678

Case Report

Dentistry Section

Diabetes and Fungal Infection- A Didactic Relationship

ISHITA SINGHAL[1], MANPREET ARORA[2], APARNA DAVE[3], PULIN SALUJA[4]

ABSTRACT

Oral fungal infections are frequently encountered in clinical practice, and with the advent of the Coronavirus Disease-2019 (COVID-19) pandemic, their incidence has quite increased. Increased emergence of oral candidal and non candidal infections is evident in patients with uncontrolled diabetes, patients on steroids or antibiotic therapies, immunocompromised and immunosuppressed individuals. Also, habits of smoking and alcohol consumption, intake of carbohydrate-rich food, and salivary dysfunction have many times influenced the colonisation of fungal infections in the oral cavity. Aspergillosis once considered exotic is now more prevalent than before and presents itself in two forms: non invasive or invasive form, which has led to the rapid dissemination of the disease. Hence, a timely diagnosis of such lesions is important to prevent their invasion into other parts of the body. This article discusses a rare case of Aspergillosis occurring in the oral cavity at the site of the extraction socket in a 50-year-old woman, who is a known diabetic without any history of COVID-19 infection. Aspergillosis unlike other fungal infections of the oral cavity has been reported more in immunocompetent individuals. Here, authors report a unique case limited to the oral cavity in an immunocompromised patient.

Keywords: Amphotericin-B, Aspergillosis, Immunocompromised patient

CASE REPORT

A 50-year-old-woman, with uncontrolled diabetes, reported to the Department of Oral Medicine and Radiology with a chief complaint of severe continuous pain and swelling in the upper left back tooth region for three months, and nasal congestion for two months. The patient was apparently normal three month ago. She did not report any history of fever, cough, body ache, or Coronavirus. She was on insulin for seven years and was not on any other medications like antibiotics or steroids. She gave a history of extraction of 26 under local anaesthesia, three month ago. After a few days of extraction, the patient experienced severe pain at the extraction site.

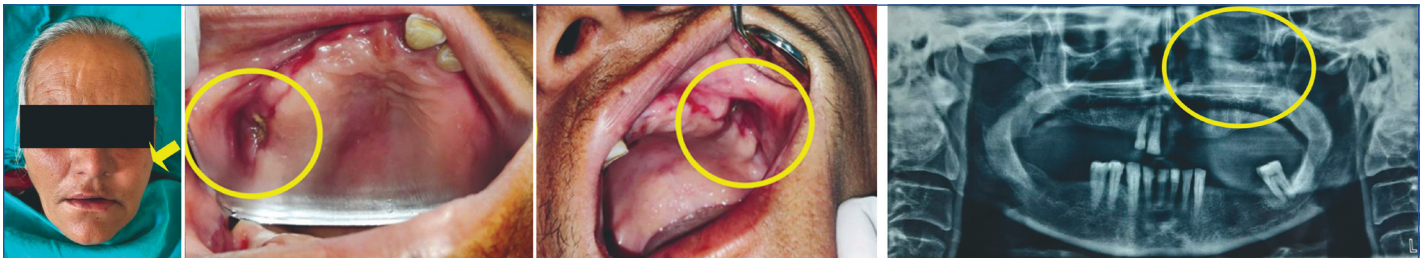
Extraorally, a diffuse, tender, and afebrile swelling were seen on the upper left-side of the face extending from the left lateral nares to the left zygomatic arch, just 2 cm below the lower eyelid, measuring approximately 3.6×5 cm, and the skin over the swelling appeared normal with no secondary changes. The swelling was firm in consistency [Table/Fig-1].

Intraoral examination revealed exposed necrotic bone at the site of the extraction socket of 26. A small well-defined swelling was also present on the anterior left region of the hard palate measuring 2×3 cm in size, with no pus discharge or bleeding. The swelling was tender and firm in consistency. The overlying mucosa of the swelling appeared blanched [Table/Fig-2].

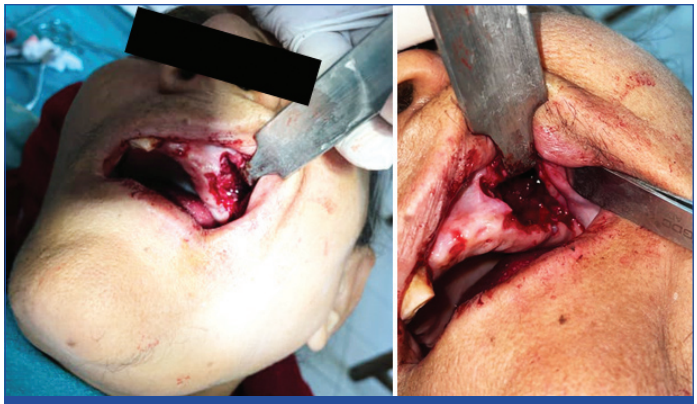
As a routine protocol, the patient was advised Reverse Transcription-Polymerase Chain Reaction (RT-PCR), haematological and radiological investigations. The RT-PCR report was negative for Coronavirus. Her blood sugar levels were raised (174 mg/dL). Orthopantomogram (OPG) indicated a diffuse radiolucency in the 26 socket and focal radiodense shadow in the paranasal sinus [Table/Fig-3]. Contrast Enhanced Computed Tomography (CECT) of the face revealed extensive bony destruction of the left maxillary sinus and left-side of the nasal cavity with marked destruction of the left side of both the hard palate and alveolar process of the maxilla. A provisional diagnosis of osteomyelitis was made with a differential diagnosis of mucormycosis and aspergillosis.

Surgical debridement and curettage of necrotic bone was done under general anaesthesia and the necrotic bone was detached from surrounding attachments and removed. A chair side 10% Potassium Hydroxide (KOH) test was performed and the report was found to be positive for septate hyphae. Then the area was irrigated with a combination of amphotericin-B powder and normal saline [Table/Fig-4].

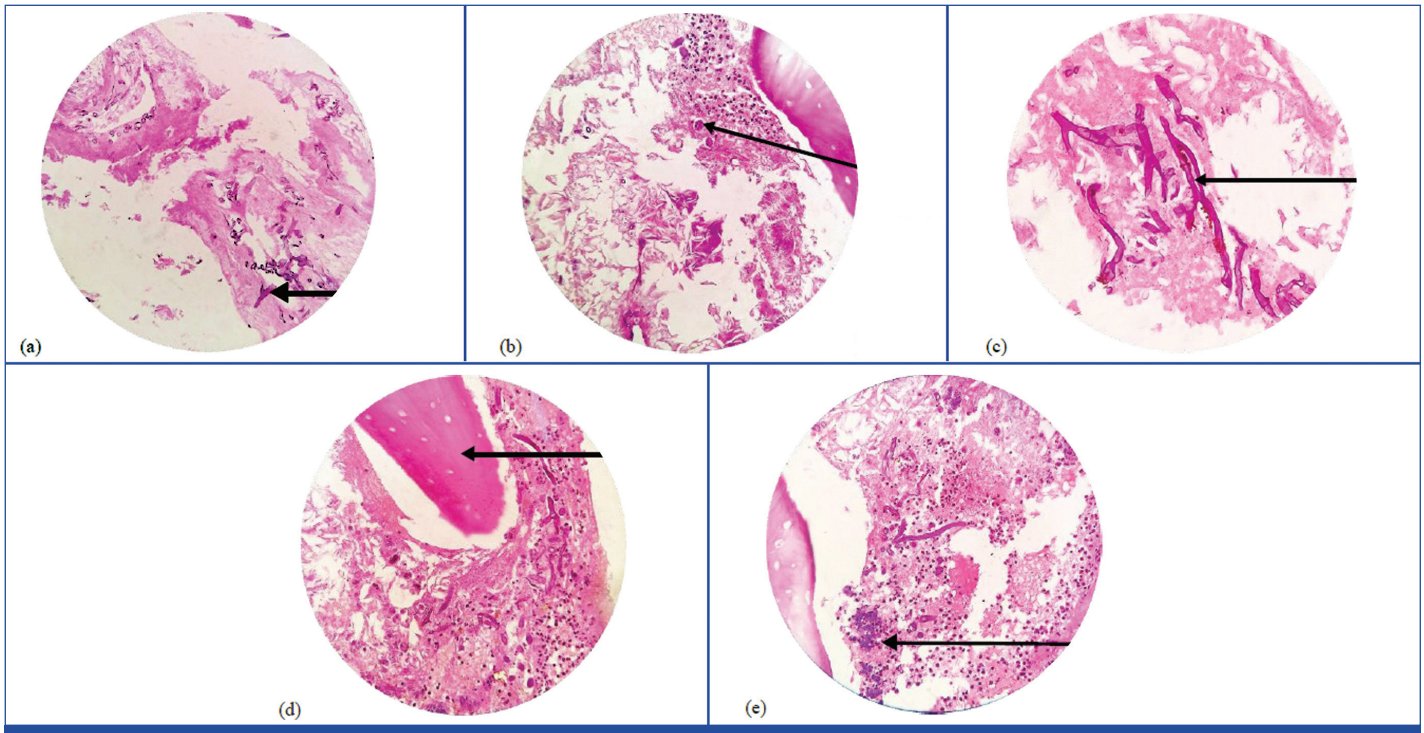
Two hard tissues and one soft tissue specimen were sent to the Department of Oral Pathology for histopathological examination. The tissue was processed for histopathological examination, which revealed bony trabeculae with empty lacunae and without any osteoblastic rimming. Marrow tissue showed septate fungal hyphae (Y-shaped), a few bacterial colonies and mild inflammatory cell infiltrate. A diagnosis of Aspergillosis was made [Table/Fig-5a-e]. The patient was prescribed injectable amphotericin-B (1 mg/kg/day) along with oral voriconazole (200 mg/twice/daily), and antibiotics



[Table/Fig-1]: Extraoral swelling present on upper left-side of the face extending from the left nares to the left zygomatic arch, just 2 cm below the lower eyelid, measuring approximately 3.6×5 cm. **[Table/Fig-2]:** Intraoral examination revealed exposed edentulous necrotic bone at the site of the extraction socket of 26. A small well-defined swelling was also present on the anterior left region of the hard palate measuring 2×3 cm in size. **[Table/Fig-3]:** Orthopantomogram (OPG) indicated a diffuse radiolucency in the 26 socket and focal radiodense shadow in the paranasal sinus. (Images from left to right)



[Table/Fig-4]: The necrotic bone was detached from surrounding attachments and removed.



[Table/Fig-5]: a) Haematoxylin and Eosin (H&E) stained tissue section revealed marrow tissue showing aseptate fungal hyphae (Y-shaped), a few bacterial colonies and mild inflammatory cell infiltrate (20X), b) Stained tissue section revealed inflammatory cell infiltrate and few multinucleated giant cells (20X), c) Stained tissue section revealed fungal colonies (40X), d) Stained tissue section revealed bony trabeculae with empty lacunae and no osteoblastic rimming (20X), e) Haematoxylin and Eosin (H&E) stained tissue section revealed (20X).

for five days. Blood sugar levels, complete blood count, and liver and kidney functions were monitored regularly. The patient was followed-up for one month. The lesion healed uneventfully, and the patient remained asymptomatic.

DISCUSSION

Even before the pandemic, the people of India were suffering from fungal infections due to its tropical climate. But now, a surfeit of COVID-19 cases, poorly uncontrolled diabetes, and the indiscriminate use of steroids such as dexamethasone have led to an upsurge of deadly fungal infections in India. These fungi are recognised as medically significant organisms, which can occur due to biological/chemical reasons and can cause potentially life-threatening diseases, with a higher risk among immunocompromised and debilitated patients, and patients with smoking habits or carbohydrate rich diets [1].

One of the second most common fungi after candidiasis is Aspergillosis, which is caused by members of the genus-*Aspergillus*. It is an opportunistic organism with more than 3,00,000 cases per annum and is ubiquitously found in decaying organic matter, compost piles, marijuana leaves, construction sites and granaries [2]. It affects both immunocompetent and immunosuppressed individuals, and can become fatal for immunocompromised patients like in uncontrolled-diabetic patients [3].

According to the International Diabetes Federation (IDF 2020), India has a large population in which an estimated 77 million people is afflicted with diabetes. Hence, India is now known as the Diabetes capital of the World [4]. Also, in the 4th edition of the Textbook of Medical Mycology, which was published in 2018, Jagdish Chander stated that "an upsurge in the number of diabetics will change the entire scenario more or less likely into an epidemic in South-East-Asia posing a very serious health threat" [5]. Due to these reasons, these fungal infections can also cause an epidemic in India.

Aspergillosis is a hypernym for a series of infections caused by the Aspergillus fungus. It is the second leading cause of death by fungal infections in hospitals. Pathogenicity of aspergillosis depends upon the fungal strain and immune status of the host. There are around 837 species of *Aspergillus*, in which the most common ubiquitous airborne species affecting humans is *Aspergillus fumigatus*, in which only pathogenic species can grow at normal human body temperature. Other species are *A.flavus, A.terreus, A.Versicolor* and *A.Niger* [2,6]. The case of aspergillosis in lung tissues was first reported by John Hughes Bennett in 1842 and in paranasal sinus by Katzenstein in 1983 [6].

Temperature and humidity are two contributory factors to the growth of fungus. The spores of aspergillus once inhaled, colonise the Peripheral Nervous System (PNS), nose, ear canals, respiratory tract, and mastoid cells, and release toxins in the blood, affecting various parts of the body like the paranasal sinuses, brain, liver, kidney, thyroid, heart, and diaphragm. Primary lesions occur in the eyes, ear and oral cavity [2,7,8]. Secondary changes like bleeding, thrombosis, and necrosis can be seen in the periodontal tissues which invade the underlying alveolar bone and further involve the cranium, causing facial edema, pain, and constant fever [9]. Pathogenicity of Aspergillosis depends upon the fungal strain and immune status of the host.

In the present case, the patient had uncontrolled diabetes, which acts as a predisposing factor. Sherashiya P et al., and Barthunia B et al., have also documented a similar case of Aspergillosis of the maxillary sinus in an uncontrolled diabetic patient [2,9]. They stated that uncontrolled diabetes mellitus alters the normal

immunologic response of the individual towards infections, due to high glucose levels, low pH, blood flow reduction, decrease in serum inhibitory activity against the pathogen and increased expression of some host receptors that mediate invasion of human epithelial cells causing abnormal phagocytosis and cell-mediated-immune abnormalities [10].

Studies have shown that patients who have undergone extraction or endodontic treatment, especially in the maxillary-posterior region are generally susceptible to oral aspergillosis [11]. The extrusion of an amalgam restoration caused a case of maxillary sinus aspergilloma, according to Burnham R and Bridle C [11]. Six gutta percha points that were unintentionally inserted into the maxillary sinus served as the aetiological agents in a case of aspergillus sinusitis that Liston PN and Walters RF described [12]. A foreign substance in the nasal cavity that resembled a plant leaf caused invasive aspergillosis was described by Syed A et al., [13]. The spores/conidia tend to invade the alveolar bone/oral mucosa through the thin lining of the maxillary sinus or gingival sulcus or open alveolar sockets, and may cause palatal or tongue lesions. Initially, it may cause localised pain and tenderness with nasal congestion, gingival ulceration, and diffuse swelling with a grey/violaceous hue. In the advanced stage, the spores penetrate the blood vessels and produce thrombosis and infarction, and hence, causing yellow-black necrotic-ulcer of the alveolar bone/palate, mobility of teeth, and destruction of sinus walls, hyper-salivation, fever and facial swelling. Once it enters the bloodstream, it can disseminate into other systemic organs like Central Nervous System (CNS), orbit, skin, liver, Gastrointestinal Tract (GIT), bone, and thyroid-gland, reaching high mortality rates [3,6,8, 10]. In the present case, the patient gave a history of extraction in the maxillary posterior-region, and complained of pain and swelling on the left-side of the hard palate with exposed necrotic bone.

A differential diagnosis of osteomyelitis or mucormycosis can be given. Aspergillosis mimics mucormycosis clinically, as they are characterised by necrosis with a dark central part or by necrotising cellulitis with the presence of papules/nodules. Both are generally predominant in diabetic patients [6,8,13]. Diagnosis is based on the characteristic symptoms present like fever, dry cough, dyspnoea, and rarely chest pain. A detailed case history with clinical evaluation, and the investigations should be performed [Table/Fig-6].

Investigations	Details
Radiographically	Aspergillosis shows the destruction of sinus walls, a focal radiodense shadow of paranasal sinuses and antrolith (a ball-shaped mass containing calcium phosphate in the center) mimicking a foreign body [8,14]. But radiographs are non specific and inconclusive, thus it should be proceeded by biopsy/culture.
10% KOH test	Aspergillosis shows hyaline septate hyphae of Aspergillus species. The hyphae are septate with dichotomous branching [1].
Histopathological examination	H&E stain shows septate hyphae which are 3-6 µm in diameter with dichotomous branching at an acute angle (~45º) in the necrotic area [5,9]. This can be differentiated from mucormycosis, which shows non septate hyphae with branching at 90º. Conidiospores and fruiting bodies are also evident [9]. Special stains like PAS stain (Periodic Acid-Schiff), Grocott-Gomori's-Methenamine-silver stain, Calcofluor white stain and fluorescent-antibody technique can also be used for confirmation [7,8]. This is the most reliable method. Immunocompetent individuals show granulomatous inflammatory response, and necrosis can be seen occasionally, whereas, in an immunocompromised patient, an inflammatory response is often weak/absent, leading to extensive tissue destruction.
Microbiological examination	Sabouraud dextrose agar is used for culturing Aspergillosis with antibiotics and without cycloheximide at 25º C and 37º C, respectively. Initially colonies of Aspergillus fumigatus appear as velvety or powdery, and then turn smoky-green. The reverse is white to tan. The conidiophore is smooth, uniseriate and parallel to the axis of the stalk [1].
Serology	It includes methods such as indirect immunofluorescent, immunoelectrophoresis, Enzyme-Linked Immunosorbent Assay (ELISA), Enzyme-Linked Immuno-Filtration Assay (ELIFA) and immunoblotting [1].
Other investigations	PCR, galactomannan assay, and B-glucan assays. These methods are expensive, highly sensitive and lack specificity.

[Table/Fig-6]: Laboratory investigations to be performed for diagnosis of aspergillosis [5].

Treatment depends upon the clinical presentation of aspergillosis and management of the patient's systemic disease. In immunocompetent patients with non invasive aspergillosis, surgical debridement can be done. For patients with allergic aspergillosis, debridement is done and corticosteroid drugs are prescribed. For patients with localised invasive aspergillosis, debridement followed by antifungal medication is indicated. In immunocompromised patients with invasive aspergillosis, aggressive debridement of necrotic tissue, combined with systemic-antifungal therapy is prescribed. Antifungal agents such as amphotericin-B, voriconazole, itraconazole and caspofungin are found to be effective in treating aspergillosis. The duration of treatment varies from six weeks to six months depending on the immunological status of the patient [6].

The prognosis of the patient always depends upon the extent and severity of the disease, the immunological status of the individual and the aggressiveness of the treatment [3]. The prognosis in immunocompromised patients is poor as compared with immunocompetent individuals, particularly if the infection is disseminated; because Aspergillosis usually develops when an immunocompromised patient is hospitalised, therefore, the ventilation system in the hospital should be monitored to prevent patient exposure to airborne spores of *Aspergillus* species.

CONCLUSION(S)

For the effective treatment of oral fungal infection, clinicians should always be aware of the patient's medical history and consider odontogenic origin. The present case report facilitates the clinicians of early diagnosis, and treatment and will also help in differentiating from other fungal diseases like mucormycosis.

Acknowledgement

Authors would like to express our gratitude to Preeti Yadav, a final year BDS student for helping us gather all the information.

REFERENCES

[1] Lenka S, Swain SK, Bhuyan R, Sahu MC. Fungal infection in the oral cavity: A Review. Int J Cur Res Rev. 2020;12(18):149-53.
[2] Sherashiya P, Ramesh N, DevGoswami R, Prasad M. A rare case of aspergillosis of the oral cavity. JOMSPB. 2016;1(1):93-103.
[3] Taneja T, Saxena S, Pandey A, Bansal V, Aggarwal P. Aspergillosis involving the maxillary sinus-a report of two cases and a brief literature review. International Journal of Oral-Medical Sciences. 2010;9(1):42-47.
[4] Oberoi S, Kansra P. Economic menace of diabetes in India: A systematic review. Int J Diabetes Dev Ctries. 2020;40(4):464-75.
[5] Chander J. Textbook of Medical Mycology, 4th ed. JP Medical Ltd; 2017.
[6] Latgé JP. Aspergillus fumigatus and aspergillosis. Clin Microbiol Rev. 1999;12(2):310-50.
[7] Krishnan PA. Fungal infections of the oral mucosa. Indian J Dent Res. 2012;23:650-59.
[8] Rajendra Santosh AB, Muddana K, Bakki SR. Fungal infections of oral cavity: Diagnosis, Management, and Association with COVID-19. SN Compr Clin Med. 2021;3(6):1373-84.
[9] Barthunia B, Kshetrapal A, Rao Y, Asif SM, Hundal KD. Aspergillosis of maxillary sinus in an uncontrolled diabetic patient: A case report. J Indian Acad Oral Med Radiol. 2017;29(4):337-40.
[10] Saluja H, Rudagi BM, Sachdeva S, Shah S, Dadhich A, Tandon P, et al. Paranasal aspergillus fungal infection in immune compromised and uncontrolled diabetic patients: A report of 5 cases along with review of literature. Clin Surg. 2017;2:1805.
[11] Burnham R, Bridle C. Aspergillosis of the maxillary sinus secondary to a foreign body (amalgam) in the maxillary antrum. British Journal of Oral and Maxillofacial Surgery. 2009;47(4):313-15.
[12] Liston PN, Walters RF. Foreign bodies in the maxillary antrum: A case report. Australian Dental Journal. 2002;47(4):344-46.

[13] Syed A, Panta P, Shahid I, Felix DH. Invasive aspergillosis associated with a foreign body. Case Rep Pathol. 2015;2015:875168.

[14] Deepa AG, Nair BJ, Sivakumar TT, Joseph AP. Uncommon opportunistic fungal infections of the oral cavity: A review. J Oral Maxillofac Pathol. 2014;18(2):235-43.

PARTICULARS OF CONTRIBUTORS:
1. Postgraduate Student, Department of Oral Pathology and Microbiology and Forensic Odontology, SGT Dental College, Hospital and Research Institute, Gurugram, Haryana, India.
2. Professor, Department of Oral Pathology and Microbiology and Forensic Odontology, SGT Dental College, Hospital and Research Institute, Gurugram, Haryana, India.
3. Professor, Department of Oral Pathology and Microbiology and Forensic Odontology, SGT Dental College, Hospital and Research Institute, Gurugram, Haryana, India.
4. Professor, Department of Oral Pathology and Microbiology and Forensic Odontology, SGT Dental College, Hospital and Research Institute, Gurugram, Haryana, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Manpreet Arora,
Professor, Department of Oral Pathology and Microbiology and Forensic Odontology, SGT Dental College, Hospital and Research Institute, Gurugram, Haryana, India.
E-mail: Manpreet.arora@sgtuniversity.org

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Nov 09, 2022
- Manual Googling: Dec 30, 2022
- iThenticate Software: Jan 25, 2023 (6%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. Yes

Date of Submission: **Nov 04, 2022**
Date of Peer Review: **Dec 05, 2022**
Date of Acceptance: **Jan 27, 2023**
Date of Publishing: **Apr 01, 2023**