

Case Analysis and Systematic Review of Aspergilloma

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ABSTRACT

Introduction: *Aspergillus fumigatus* is the most prevalent fungal pathogen reported to cause diseases such as aspergilloma or aspergillosis in humans. Aspergillomas are commonly seen in a poorly drained and avascular cavitary space. Paranasal sinuses are most commonly involved, especially maxillary sinus. In the past two decades, the incidence of aspergillosis has increased substantially.

Aims: To evaluate cases reported as aspergilloma of the maxillary sinus and to determine the percentage of cases involving aspergilloma of the maxillary sinus in healthy individuals.

Materials and Methods: After the final full-text review, 16 articles were included in this systematic review. Data extracted from these full-text articles was reviewed.

Results: 83 % of cases had a history of dental procedures, with 42 % of those being due to infection from previous extraction sockets and 41 % due to root canal therapy (RCT). About 43% of the patients were immunocompromised, while 56% were healthy without any predisposing conditions.

Conclusion: *Aspergillus* fungal infections of the paranasal sinuses are common and can occur in apparently healthy as well as immunocompromised individuals. Aspergilloma is the most common fungal infection involving the maxillary sinus with iatrogenic-dentogenic factors being predominant for initiation and progression of the infection. About 43% of the patients in this review were immunocompromised patients whereas 56% of the patients were healthy without any known predisposing conditions. The progression and prognosis of this disease depends on the location and immunologic status of the patient. So, it is very important for dentists to be cautious while performing any dental procedures so as not to initiate any iatrogenic infections.

Keywords: aspergilloma, case report, aspergillosis, mycetoma, maxillary sinus, odontogenic infection, dental treatment.

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INTRODUCTION

Opportunistic fungal infections of the oral cavity are most commonly caused by candida species. The second most common infection is by *Aspergillus fumigatus* species.¹ *A.fumigatus* belongs to the ascomycetes class of saprophytic fungi that are normally avirulent in healthy individuals but are capable of causing infections in both immunologically competent and in immunocompromised individuals.² Hence it is a truly opportunistic pathogenic fungus and also one of the most common widespread airborne saprophytic fungus causing infection.³ Its spores and conidia are found in the environment and once the organism gains entry into the respiratory tract, it spreads by its hyphae, and releases toxins.⁴ When the conidia are restricted within the lungs for a longer period of time, it gradually causes infection and also, is capable of disseminating to various sites through blood and endothelial lining by releasing the toxins.⁴ *A.fumigatus* releases various toxins such as hemolysin, aflatoxin, gliotoxin, and phthalic acid.⁵ *A.fumigatus* is solely responsible for causing sinus aspergillosis. Aspergilloma is a subtype of aspergillosis, commonly referred to as "fungus ball" or "mycetoma".⁶ Deve in 1938 was the first person

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to describe an aspergilloma and named it "mycetoma".³ Belcher and Plummer formulated the classification of aspergilloma in 1960 as simple aspergilloma and complex aspergilloma. Aspergilloma appears as a large, expansile mass, without the involvement of the underlying mucous membrane.⁷ It is commonly appreciated in body cavities

such as lungs, paranasal sinuses, especially the maxillary sinus antrum with palatal perforations more common in oral considerations. The main predisposing factors of development of aspergilloma are preexisting pulmonary disorders, chronic debilitating conditions, and immunosuppression. It is usually asymptomatic and may take several years for the symptoms to occur.⁸ Even though it is asymptomatic in the majority of the cases, hemoptysis is the most common clinical manifestation in symptomatic patients. Aspergilloma mainly affects individuals with pre-existing lung disorders such as tuberculosis, sarcoidosis, bronchiectasis, cystic fibrosis and systemic immunodeficiency.⁹ The global prevalence of aspergilloma over a period of 5 years is estimated to be 18/100000.¹⁰

The main objective of this paper is to discuss the etiology and management of odontogenic maxillary sinus aspergilloma, as well as to present new cases and review previously published cases.

CASE PRESENTATION

A 25 year old male reported to Saveetha Dental College & Hospitals with a complaint of pain in his left maxillary region,

which was mild and localized with the presence of notable nasal discharge for the past 10 months. The nasal discharge was thick, yellowish in color, and was appreciated every 10-15 minutes. Also 2 years earlier had undergone an orthognathic surgery (Anterior maxillary osteotomy and Bilateral sagittal split osteotomy) with fixation of mini plates and screws, due to an accident. He was not under any medications and had no history indicative of immunodeficiency. The family and occupational histories did not reveal any significant findings and there were no known drug allergies. On examination and palpation, the maximum size of the lesion was that of the entire maxillary sinus and also, the patient experienced tenderness extending from the philtrum of the lip up to the left zygoma. Extraoral and intraoral examinations revealed no evident swelling. Radiographically, the OPG showed radiopaque haziness in the entire left maxillary antrum. Further CT scan showed the hyperdense area with breaching of cortical bone involving the anterolateral wall of the left maxillary sinus (Figure 1). The patient underwent debridement and sinus exploration of the left maxillary sinus along with the removal of mini plates

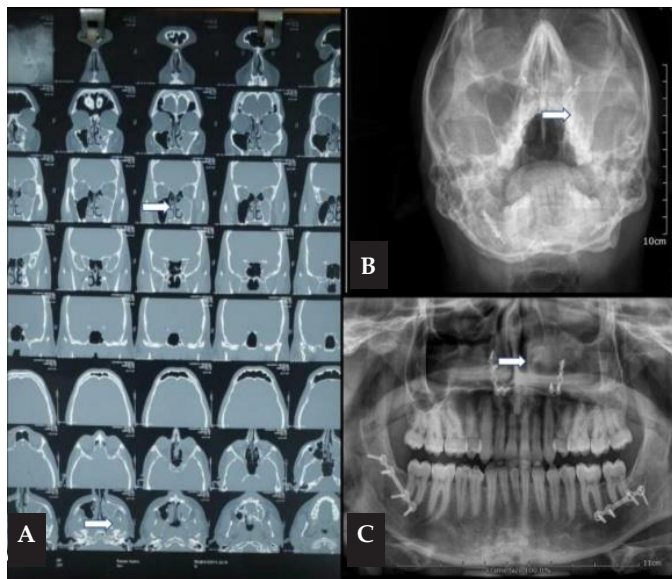


Fig. 1: Representing (A)- CT SCAN-hyperdense area involving the anterolateral wall of the left maxillary sinus, (B)- PNS VIEW-showing radiopaque haziness, (C)- OPG-showing radiopaque haziness in left maxillary region

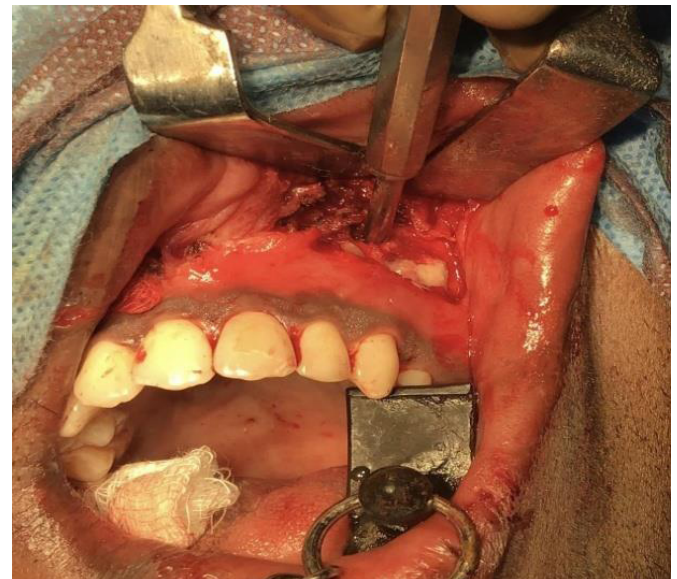


Fig. 2: Represents the clinical image showing the debridement and sinus exploration in the left maxillary sinus along with the removal of mini plates

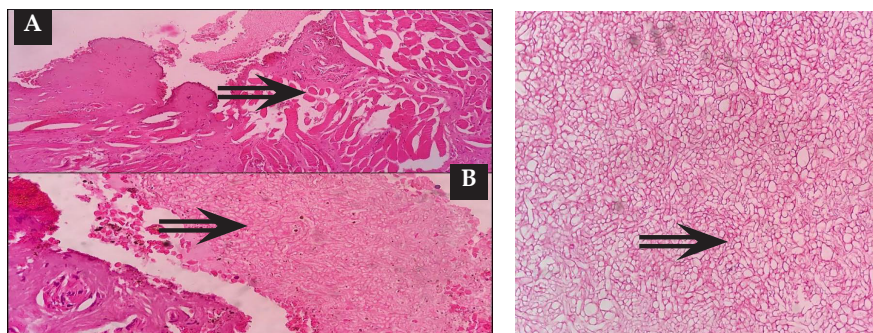


Fig. 3: Represents the H&E image of Aspergilloma in maxillary sinus cavity in A- 10X; B- 40X magnification; C- 100X magnification - Abundant tightly packed septate hyphae branching at acute angles - Aspergilloma

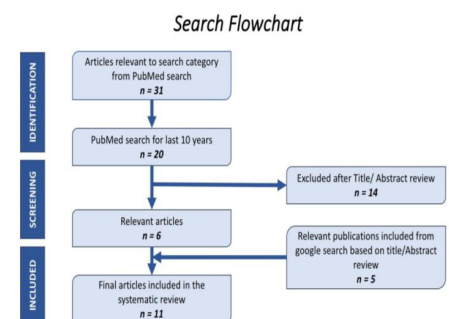


Fig. 4: Demonstrating the process of selection of articles from PubMed, Google search, manual search, and cross-reference of articles.

and screws to prevent further possible infections. (Figure 2). After surgery, the samples were sent to the department of Oral & Maxillofacial Pathology. The histopathological examination of the resected specimen was performed. Hematoxylin and eosin-stained sections showed densely packed fungal hyphae in several areas giving an appearance of a mass/ball suggestive of fungal infection -Aspergilloma (Figure 3). There was hypertrophic pseudostratified ciliated columnar epithelium with the underlying dense connective tissue stroma showing abundant filamentous tightly packed septate hyphae branching at 45-degree acute angles within inflammatory exudates and cell debris. Routine blood investigations were normal. According to the patient's history and clinical study, the patient was prescribed analgesics and antibiotics. A 1-year follow-up was done until the patient became asymptomatic.

MATERIALS AND METHODS

This review was done in accordance with Preferred Reporting Items for Systematic Reviews¹¹ and Meta-analysis of Observational Studies in Epidemiology statement.¹² We carried out a systematic review according to the Cochrane Handbook 13 reporting guidelines that will be used to conduct and report data synthesis, respectively.

Identification of literature:

We conducted a systematic literature search online in PubMed, Cochrane Library, and SCOPUS database till January 2020.

We also carried out google internet search using keywords aspergillosis, aspergillus, aspergilloma, fungus ball, mycetoma, maxillary sinus, odontogenic, and dental, as well as combinations thereof. Ethical approval was not needed because of this secondary study of the previously published studies. One reviewer obtained the full texts of relevant articles following the search and inspection of titles and abstracts of citations to identify those articles of the case reports that presented aspergilloma or aspergillosis in maxillary sinus cavities was included in this study. The titles and the abstracts were reviewed. The text of the selected case reports was retrieved and further analysed.

Search methodology:

The search methodology applied in PubMed was by using the keywords: (Aspergillosis) or (Aspergilloma) and (Maxillary sinus) or (Maxillary antrum) and (Case report) Filter: last 10 years.

Case reports with aspergilloma or aspergillosis reported in the maxillary sinus published in the English language in the last 10 years (2010-2020). The CARE guidelines were followed by two independent reviewers to assess the quality and each article was also assessed according to the guidelines provided by the author.

RESULTS

The initial search yielded 31 results. Additional filters were added for restraining the search to last 10 years (2010-2020), yielding 20 results. 14 articles were excluded based on the exclusion criteria, title, and abstract screening reviews. 6 articles were approved for full-text review from PubMed search. An additional 10 articles were included from Google search, manual search and cross-references. After the final

full-text review, 16 articles were selected for this systematic review.^{15,16 17,18,19,20,21,22,23,24} Data from the full-text articles was selected, reviewed and content extracted.^{25,26,27,28,29}

The accuracy of the primary data extracted from each study was independently verified. Collected data consisted of the following: age, sex, site, medical history, radiographic findings, treatment done and follow up (Table 1) from studies performed from 2010-2020. Around 60% of aspergilloma or aspergillosis cases were seen in males compared to 40% in females and mean (SD) age of the patients was 40.9 years. 12% of cases had bilateral maxillary sinus aspergilloma, and 88% involved unilateral maxillary sinus with left maxillary sinus involvement more common. About 83% of the cases showed a previous history of dental procedures, of which 42% were due to infection from previous extraction sockets and 41% due to RCT. About 43% of the patients were immunocompromised while 56% had no known predisposing conditions. In all the included studies, the standard treatment was Caldwell-Luc surgery followed by antifungal therapy and all cases showed complete recovery within 3-12 months of follow-up.

Quality Assessment:

According to the CARE GUIDELINES, in 10 out of the 16 case reports insufficient information was provided in the follow up period (item 10) followed by the item 12 and 13 which included the patient's consent form and the prospective review of the patient which were not available in all the case reports. In 8 of the reports there was no evidence of keywords (item 2) and there was inadequate information about the uniqueness of the article in the introduction (item 3).³⁰

DISCUSSION

Generally, Aspergillus infection is believed to be an opportunistic pathogen that is commonly seen in maxillary sinus due to the indirect inhalation of the spores of aspergillus species from the environment mixed with dust.²⁸ About 10% of the case with sinusitis was found to be aspergilloma, predominantly in maxillary sinus.²⁹ Iatrogenic infection can also cause infection in the maxillary sinus developed from any underlying dental procedures. Advanced imaging technique provides a good diagnostic background for the detection of aspergilloma in the maxillary sinus. Histopathologic examination is considered to be the most reliable and accurate test to diagnose aspergilloma but it can be a slow process.^{30,31,28} The standard management of aspergilloma in maxillary sinuses is surgical debridement to remove all necrotic, devascularized tissue and systemic antifungal therapy to reach the involved site.³²

Effective surgical treatment requires adequate exposure to remove all necrotic, devascularized tissue with the ultimate purpose to permit the antifungal agent to reach the involved site.³³

The present case report and the studies included within this review had typical characteristics of aspergilloma or aspergillosis. In this case report and systematic review of 16 case reports, we found that about 60 % of aspergilloma or aspergillosis cases occurrence were seen in male patients, when compared to 40% cases found in female cases which is consistent with the previous study by Rajeev et al who identified aspergilloma in 41 cases showing male predominance, half of the patients were in the fourth decade. Most of the current



literature on aspergilloma has been a surgical series showing slight male predominance. Patients who are exposed to the spores of aspergillus species under favourable conditions at any age can develop aspergilloma or aspergillosis. The cause of the gender difference is unknown.

Interestingly, there are very few cases that are reported with bilateral maxillary sinus or multiple paranasal sinus involvement. Maxillary sinus aspergilloma is usually seen unilaterally, and bilateral lesions are very rare. 12% of the cases in this review were reported to have bilateral maxillary sinus aspergilloma, and all other cases (88%) had unilateral maxillary sinus aspergilloma, with left maxillary sinus more common similar to the case report discussed above. Our results are in accordance with previous literature reported by Vinciguerra et al, a case of bilateral maxillary-ethmoidal sinus aspergilloma that occurred after bilateral endodontic treatment. This can be due to the dental procedures that can perforate the sinus membrane and cause mucociliary paralysis and mucosal hyperemia, resulting in epithelial dysfunction in the maxillary sinus.²⁰

The main predisposing factor for maxillary sinus aspergilloma was dental procedures like root canal therapy, extraction, filling, or grafting procedures which are exhibited as localized and mild pain. The current case report and the included review articles showed that about 83% of the cases showed a previous history of dental procedures, in that 42% were due to infection from previous extraction sockets, and 41% due RCT. Similarly, several cases of aspergilloma in the literature have been detected in sinuses that had been perforated by a previous dental procedure, while the contralateral side remained unaffected.

Aspergilloma is commonly underestimated in clinical care because the infection only becomes symptomatic after a long period of fungal contamination. About 25% of the aspergillomas were diagnosed after 1 year, after the onset of symptoms. This result is consistent with the previous literature by Giardino et al, a case of aspergilloma that arose 2 years after root canal therapy. In another case, Sohn et al reported a case of *Aspergillus* 1 year after the patient had undergone sinus bone grafting. However, occasionally, the time of onset of the infection was shorter.^{34,35,36,37,38} This is because of the non-invasive character and slow progression of the lesion. So, it is critical to ensure adequate follow-up after dental treatment involving the maxillary sinus.

Aspergilloma has been reported in healthy as well as immunocompromised individuals. About 43% of the patients in this review were immunocompromised patients whereas 56% of the patients were healthy without any known predisposing conditions including our case which showed aspergilloma involved in a healthy individual. Aspergilloma has been found to be increasing over the last several years and has been associated with an increase in the number of patients with some form of immunodeficiency.³⁹ The progression and prognosis of these diseases depend on the location and immunologic status of the patient; and the possibility of invasive aspergillus infections is higher due to compromised immunity. The fungus enters the lung through the bronchi and produces localized bronchitis. The fungus then infiltrates through the pulmonary wall into the adjacent pulmonary artery, producing thrombosis and infarction. As the fungi proliferate rapidly through the hemorrhagic and infarcted lung, they induce an expanding

infarct.

Panoramic radiographic examinations are a straightforward way to evaluate the maxillary sinus bilaterally for the diagnosis of aspergilloma.⁴⁰ In our review, in the majority of cases computed tomography and panoramic radiographic imaging technique were used. The more detailed examination with computed tomography (CT) may be necessary to exclude other sinus diseases, such as antrolith, osteoma, mucocele, B cell lymphoma, squamous cell carcinoma, adenoid cystic carcinoma and inflammatory myofibroblastic tumors form the differential diagnosis.⁴⁰ The extent of the lesion, bone involvement, and erosion can also be evaluated using CBCT, which requires a lower radiation dose, is cost-effective and less time-consuming.

Aspergilloma is a fungal infection that carries a very good prognosis with surgical debridement, usually a Caldwell-Luc procedure followed by an antifungal regimen. All the reported cases showed complete recovery within a time period of 3-12 months of follow-up. Also, there were no records of recurrence of fungal infection after the standard treatment protocol. If symptoms persist for a long time after surgery, an oral antimycotic drugs may be required as additional therapy.³⁷ Nonetheless, clinicians should be careful about using these drugs because of severe adverse effects, such as nephrotoxicity.³⁸ Since bacterial superinfection can cause acute sinusitis attacks, appropriate antibiotic therapy is recommended in order to avoid bacterial coinfections.³⁹

Dental procedures that involve the maxillary sinus may make it easier for fungal sinusitis to develop, which is similar to other sinus infections. Clinicians should be aware of the possibility of a fungal etiology, particularly in cases that are resistant to treatment, and should monitor patients if sinus perforation occurs during a procedure to reduce the risk of infection. The limitations of our review are its restriction to English-language publications and the difficulty in assessing some case reports because they lacked detail.

CONCLUSION

The clinical conclusions from the review and our reported case show that the maxillary sinus is the most common site of all the paranasal sinuses for aspergilloma, with mild and localized pain being its common symptom. The confirmatory diagnosis of aspergillus infection can be established by histopathological examination of routinely stained Hematoxylin and eosin sections. Surgical debridement followed by an antifungal regimen is the therapy of choice in cases of aspergillosis maxillary sinus infection.

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