

# DESTRUCTIVE NON-INVASIVE INFECTION IN ISOLATED FRONTAL SINUS ASPERGILLOMA: REVEALING PREVALENCE AND PROPOSITION OF A NEW PATHOGENETIC MODEL.

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## Abstract

**Objectives:** The aim of this study is to report our cases of isolated frontal sinus aspergilloma (FSA), and identify key features and aspects suggestive of this pathology. **Moreover,** we have investigated the pathogenesis of this FSA, which has not been clearly elucidated yet. **Materials and Methods:** A retrospective study on cases of isolated FSA treated at the unit of Otolaryngology of the Hôpital Lariboisière in Paris from 2009 to 2023 was performed. A chart review was done, Demographic and radiologic data, type of treatment with intraoperative findings, and follow-up were analyzed. **Moreover,** a literature review was carried out on Pubmed and Scopus using the search terms “frontal sinus aspergilloma”, “frontal sinus fungus ball” and “frontal sinus mycetoma”. **Non-invasive FSA characteristics,** especially the relation with surrounding bony structures were analyzed. **Results:** Six patients were included. The median age of the patients was 58 years old (range 25-69); 2/6 patients were female. The most common symptom was headache. All the patients underwent exclusive endoscopic sinus surgery. **With regards to literature review,** 17 papers have been identified reporting a total number of 30 cases of FSA. **Overall,** frontal sinus walls erosion was described in 47% of the cases showing a prevalence of erosive behavior of this pathology. **Conclusions:** FSA shows a higher incidence of bone erosion compared to other PSA. The destructive behavior of FSA could increase the risk of potential intracranial and intraorbital complications. **Recognizing the radiological features of FSA,** is crucial for accurate differential diagnosis with invasive forms of fungal infections and treatment planning.

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## Introduction

Aspergillosis of the paranasal sinuses (PSA) is a well known entity, which usually occurs in the maxillary sinus. Frontal sinus is rarely involved, and usually represents the progression of a mycotic infection within other sinuses. However, isolated involvement of frontal sinus even though extremely rare, has been reported, but its pathogenesis poorly understood [1]. Computed tomography (CT) and/or magnetic resonance (MR) imaging are the gold standard in the diagnostic process. Radiological aspect of frontal sinus aspergilloma (FSA) is similar to other PSA, except for a high incidence of erosive non-invasive forms [1].

The aim of this study was to report our cases and identify key features and aspects suggestive of FSA, to

enable clinicians to appropriate diagnosis; moreover, we have investigated the pathogenesis of this entity which has not been clearly elucidated yet.

## Methods

A retrospective study on cases of isolated FSA treated at the unit of Otolaryngology of the Hopital Lariboisière in Paris from 2009 to 2023 was performed following STROBE guidelines. A chart review was done, Demographic and radiologic data, type of treatment with intraoperative findings, and follow-up were analyzed. Moreover, a literature review was carried out on Pubmed and Scopus using the search terms “frontal sinus aspergilloma”, “frontal sinus fungus ball” and “frontal sinus mycetoma”. All returned items were filtered for relevance and English language. Relevant clinical information from the literature was subsequently pulled and tabulated for review with further datasets from our own case series (*Tab 1-2*). Geographic distribution of the cases presented in the literature was reported and the Koppen climate classification system was used to estimate environmental and climatic conditions.

## Results

Six patients were included. The median age of the patients was 58 years old (range 25-69); 2/6 patients were female. Among all patients, only one was immunocompromised due to heart transplantation. The right frontal sinus was involved in 1/6 patients, one of them reported bilateral infection. The most common symptom was headache; one patient was referred to our center for persistence of FSA after two endoscopic procedures performed in other centers.

All the patients underwent preoperative CT and/or MR imaging. Non-invasive FSA characteristics, especially the relation with surrounding bony structures were described (Tab 1). Six patients underwent exclusive endoscopic sinus surgery with a complete removal of the material, which was sent for pathologic and microbiologic evaluation to confirm the presence of fungal hyphae and mycotic colonization in the culture. A biopsy of the health mucosa of the frontal sinus was also performed and excluded fungal invasion. In one case (patient n. 5) a revision surgery was performed for a stenosis of the frontal sinusotomy which occurred 11 months after the initial surgery (Tab 1). All of them were followed with endoscopic control with a median of 71 months (range 13-240), no recurrences of FSA have been reported.

With regards to literature review, 17 papers have been identified reporting a total number of 30 cases of FSA. We analyzed data on geographic provenance of the patients, symptoms, radiological findings focusing on the presence of bone damages, surgical treatment and recurrences (Tab 2).

## Discussion

The main finding of the present study is that, in contrast with other PSA, FSA exhibits a distinctive prevalence of bony wall remodeling. In particular, it is characterized by a higher incidence of bone erosion (47% according to our findings, versus 37.8% in maxillary sinus [2], 13-52% in sphenoid sinus [3] and incidence not established for ethmoid sinus due to the rarity of the location), suggesting a potentially higher number of complications in this subsite. Moreover, we provide a new element to understand the pathogenesis focusing on temperature variations within sinuses and the impact on spore's proliferation, which could explain the rarity of frontal sinus involvement in PSA. To our knowledge, this is one of the largest single center case series reported and it's the first paper in which a new hypothesis has been advanced to explain the peculiarity of this entity.

The pathogenesis of PSA poses a unique challenge, with *Aspergillus fumigatus* being one of the most common isolated spores and common component of daily respiratory exposure. Despite inhaling over 100 *A. fumigatus* conidia/m<sup>3</sup> daily, not all lead to PSA, indicating a multifactorial origin involving host factors, environmental influences, and fungal elements. The maxillary sinus is most frequently involved, followed by sphenoid, while frontal aspergillomas occurrences are rare [2]. Different hypotheses attempt to explain varied PSA distribution within sinuses. Nicolai et al. linked maxillary sinus aspergilloma to prior endodontic treatments,

suggesting that dental sealers and an anaerobic sinus habitat promote inflammation and fungal growth [2]. Conversely, considering the other paranasal sinuses, the only hypothesis advanced by other authors explaining the occurrence of aspergilloma is the aerodynamics theory. The latter, especially for the frontal sinus, conceive that the anatomical complexity and location of the sinus makes it less accessible for the inhaled spores compared, for example with the sphenoidal sinus [1]. However, the peculiar anatomy of the spheno-ethmoidal recess alone do not explain the higher incidence of aspergilloma within sphenoid sinus compared to the frontal sinus. Indeed, attention has been put on the mucociliary drainage pathway, which is likely to convey spores in remote areas of the sinuses, justifying the presence of hyphae in these peculiar subsites. This theory, together with investigations into *A. fumigatus* optimal growth conditions have been enquired to justify the difference pattern of incidence within paranasal sinuses, highlighting temperature and pH as crucial factors [4]. It remains unclear whether these elements are influenced by the climate conditions rather than patient's microenvironment within paranasal sinuses. However, the ubiquity in the geographic distribution of the reported cases suggests that paranasal sinus microenvironment is more reliable in explaining the differences and the rarity of non-maxillary PSA. In this context, the higher incidence of sphenoid fungus balls may be due to its central head position, surrounded by internal carotid arteries and cavernous sinuses, maintaining a higher temperature. Conversely the frontal sinus shows as main boundaries the outer surface and the brain, leading to lower temperatures within the sinus and creating a less favorable environment for spore proliferation, justifying its sporadic involvement.

Due to the rarity of frontal sinus involvement in PSA, we have investigated whether this location was not only peculiar in terms of prevalence and pathogenesis, but mostly in terms of behaviors. General paranasal sinus aspergilloma is a non-invasive form of paranasal fungal sinusitis, but cases showing a more aggressive behavior causing bone erosion without histological evidence of tissue invasion have been reported [5]. In these cases, erosion of the sinus walls refer to the expansion and thinning of the bony wall of the sinus because of the pressure caused by hyphal proliferation and necrosis. The general incidence of erosive non-invasive forms of PSA range though 2.2-63%, with different incidences between the paranasal sinuses and the possibility of different complications depending on the proximity of the adjacent structures [2; 6; 7]. According to our findings, frontal sinus walls erosion was described in 47% of the cases. Only Gupta et al. specifically commented on the occurrence of bony destruction of the sinus walls, which involved exclusively the posterior plate and/or the floor of the sinus [8]. The consequence and eventual complications of bony destruction depends on the anatomical structures adjacent to the sinus. Nevertheless, contrarily to sphenoid sinus aspergilloma, in which the skull base erosion has been reported to have a clear link with the occurrence of the intracranial and intraorbital complications, a clear relation between frontal sinus wall destruction and the occurrence of complications has not been established [3]. Uri et al. were the only authors to compare patients with erosive FSA with patient with non-erosive FSA, reporting a more violent clinical course for the first [9]. Sporadic cases of intracranial or orbital complications such as orbital cellulitis have been described, and the high incidence of the destructive bone pattern can explain that proptosis secondary to orbital erosion is the initial clinical manifestation in 37.5% of the cases [8; 10]. However, these findings were not confirmed in our cohort, since none of our patients experienced intracranial or intraorbital complications and the small number of cases in the literature did not permit to compare the two groups.

When dealing with erosive FSA, differential diagnosis with invasive forms of chronic fungal sinusitis is mandatory since the bone erosion could be the manifestation of tissue invasion. On this purpose, biopsy of the tissue is mandatory to exclude tissue invasion at the histopathological examination [2]. Once diagnosis of FSA has been advanced, surgery is the treatment regardless the presence of symptoms to avoid potential complications, due to the high incidence of erosive forms and the relations of the frontal sinus with orbit and the brain.

The main limitation of this study arises from its retrospective character and the associated bias.

## Conclusions

Frontal sinus aspergilloma shows a higher incidence of bone erosion compared to other PSA. The destructive behavior of FSA could increase the risk of potential intracranial and intraorbital complications. Recognizing

the radiological features of FSA, is crucial for accurate differential diagnosis with invasive forms of fungal infections and treatment planning.

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## Tables:

### Hosted file

image1.emf available at <https://authorea.com/users/764002/articles/741517-destructive-non-invasive-infection-in-isolated-frontal-sinus-aspergilloma-revealing-prevalence-and-proposition-of-a-new-pathogenetic-model>

*M: male, F: female, CT: Computed Tomography, MRI: Magnetic Resonance Imaging, FU: Follow UP, NA: non available data*

Table 1. Patients informations

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image2.emf available at <https://authorea.com/users/764002/articles/741517-destructive-non-invasive-infection-in-isolated-frontal-sinus-aspergilloma-revealing-prevalence-and-proposition-of-a-new-pathogenetic-model>

*RX: Radiography, FNAC: Fine Needle Aspiration Cytology, CT: Computed Tomography, MRI: Magnetic Resonance Imaging, FU: Follow Up*

Table 2. Review of the literature