

A Case of Fungus Ball-Type Maxillary Sinusitis Due to *Penicillium Roqueforti*

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Abstract The *Penicillium* genera, encompassing about 225 different species of fungi, are naturally present in the environment. These genera are poorly linked to human disease, except for *Penicillium marneffei* causing septicemia in immunocompromised hosts. Thus, *Penicillium* species recovered from respiratory tract samples are often considered as inhaled contaminants in the clinical laboratory. However, we report here a case of fungal maxillary sinusitis due to *Penicillium roqueforti* diagnosed in a 40-year-old female, a teacher, complaining of moderate pain for months in the maxillary sinus and chronic posterior rhinorrhea. CT scanner and MRI enabled a preliminary diagnosis of left maxillary fungus ball-

type sinusitis with calcified material seen on CT and marked very low signal in T2 weighted images seen on MRI. Anatomopathological and mycological examination of sinusal content showed septate hyphae. Direct sequencing of the sinusal content revealed *P. roqueforti*. *P. roqueforti* has been traditionally used in France for more than 200 years for cheese ripening. However, to our knowledge, this ascomycetous fungus has very rarely been associated in the literature with human disease. *P. roqueforti* is associated only with cheese worker's lung, a hypersensitivity pneumonitis affecting employees in blue cheese factories. Other species in the *Penicillium* genus are reported to cause various disorders such as invasive infection, superficial infection or allergic diseases. *P. roqueforti* has never previously been reported as a cause of human infection. Thus, we report the first case of fungus ball due to *P. roqueforti* in an immunocompetent patient.

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Introduction

Fungus balls in the paranasal sinus cavities are defined as masses of fungal filament in a sinus cavity. Fibrinopurulent and/or necrotizing material surrounding the fungal mass is often described as a result of the inflammatory response [1]. *Aspergillus* species

represent more than 60% of the fungi recovered from fungus ball [2, 3]. However, during the last decade, new species have emerged in fungus ball, such as *Schizophyllum commune* or *Cochliobolus hawaiiensis* [4, 5]. *Penicillium* species have been associated with roughly 10% or less of fungus balls in the literature, but no studies have accurately identified the *Penicillium* at species level [1, 2]. *Penicillium roqueforti* is a common saprotrophic fungus of the Trichocomaceae family. Widespread in nature, it can be isolated from soil, decaying organic matter and plants. This species has been traditionally used for many years to ripen blue cheese. It is implicated in pathogenic diseases in humans, but has never been described in fungal sinus pathology. To our knowledge, we report here the first case of fungus ball due to *P. roqueforti*.

Case Report

A 40-year-old female teacher residing in Marseilles, France, was referred to our Department of Oto-Rhino-Laryngology and Head and Neck Surgery for «maxillary sinusitis». She had experienced moderate pain at the left maxillary sinus and chronic posterior rhinorrhea for several months. She had no fever, no anosmia, no nasal bleeding. Her medical history was insignificant and included glaucoma and cataract, treated by her ophthalmologist. Laboratory values were all normal.

Compute tomography scanner (CT) and magnetic resonance imaging (MRI) enabled a preliminary diagnosis of left maxillary fungus ball-type sinusitis with calcified material seen on CT and marked low signal in T2-weighted images seen on MRI (Fig. 1). No oro-antral communication or migrated metal dental filling was seen on CT.

The patient underwent functional endoscopic sinus surgery (FESS) aimed to remove all the sinus content (inferior and middle meatal antrostomy procedures). We found an accessory inferior meatus in front of the fungus ball. Macroscopic appearance was that of a classic fungus ball. Sinus mucosa showed no sign of invasive disease. Anatomopathological and mycological analyses were performed on the removed sinus content.

Histopathologic examinations after periodic acid Schiff and Gomori-Grocott stain revealed septate hyphae forming a fungus ball surrounded by

inflammatory material. Mycological examination after lactophenol blue staining (Lactophenol blue solution, Sigma-Aldrich, France) of an apposition of the intrasinus content also showed septate hyphae [6]. Several fragments of the sinus content were inoculated on a Sabouraud-Gentamicine-Chloramphenicol plate (Oxoid, Dardilly, France) incubated at 30 °C for at least 10 days. However, the samples failed to grow in culture. DNA sequencing was performed in parallel directly on the sinus content, as described by Normand et al. [7]. The sinus content was dilacerated and then incubated overnight with proteinase K at 56 °C. DNA extraction on the supernatant was done using the automated NucliSENS® easyMAG system for nucleic acid extraction. The partial beta-tubulin gene was amplified using the following primers: Bt2A–GGT AAC CAA ATC GGT GCT GCT TTC and Bt2B–ACC CTC AGT GTA GTG ACC CTT GGC. Amplification started with a first denaturation step at 94 °C during 10 min, followed by 40 cycles of a 20-s denaturation step at 94 °C, then a 30-s hybridization step at 58 °C and a 60-s elongation step at 72 °C. The final elongation step lasted 420 s at 72 °C. Sanger sequencing was performed using a 3130 Genetic Analyzer (Applied Biosystem, Inc., Courtaboeuf, France). Sequence assembly was performed using the Sequencer software. The 869-bp contig obtained showed a 99% identity match with the Genbank sequence accession number AY674382.1.

Discussion

Fungus ball is the most frequent noninvasive fungal rhinosinusitis and incidence has increased over the past two decades [8]. Fungus sinuses are mainly reported in the maxillary sinus but may also be found in sphenoid, frontal or ethmoid sinuses [9]. Most fungus balls remain a mild disease in immunocompetent patients. However, complicated cases have also been described in immunocompromised patients [10].

As in bacterial sinusitis, mucocoele or neoplasm, the radiographic presentation of paranasal sinus fungus ball shows localized opacity of a paranasal sinus [11]. The combination of CT and MRI is useful to assess fungus ball. Typical imaging findings on CT scanner consist in a hyper-attenuating ball with calcific foci within the opacity [12]. Central metal dental fillings may also be seen. As in mucocoele, fungus balls usually

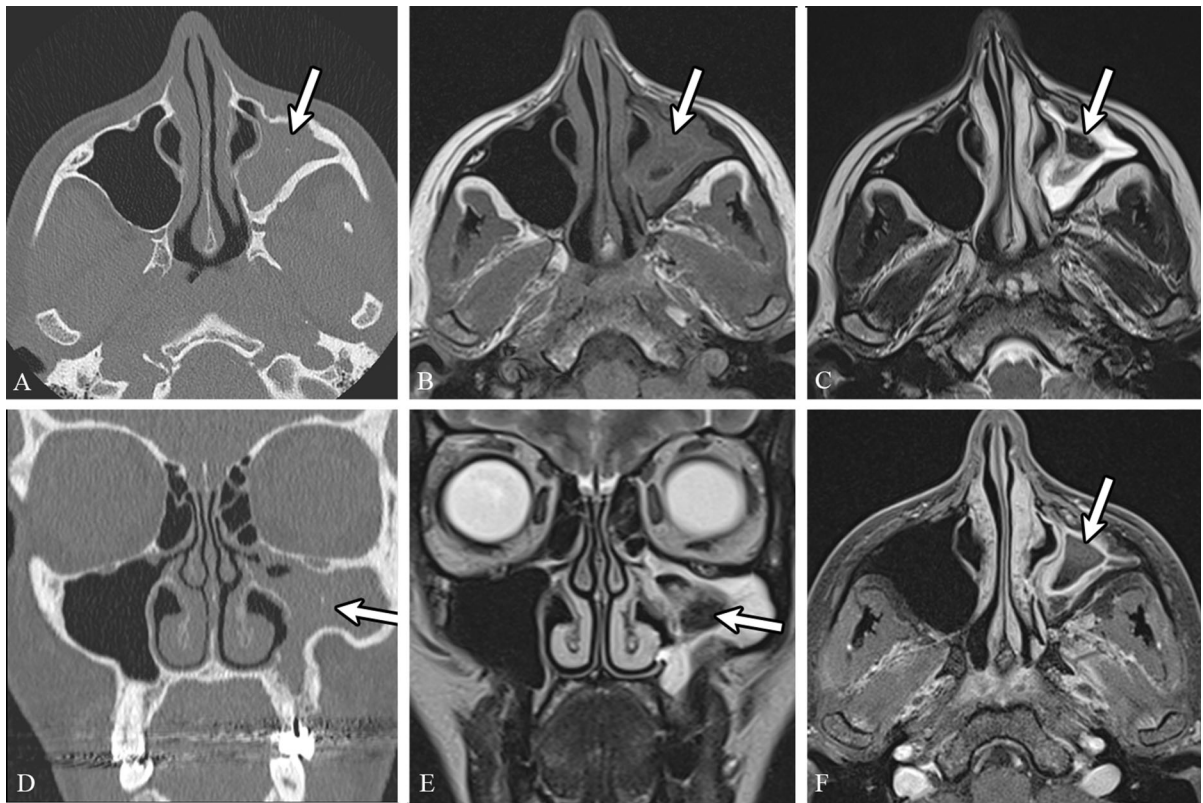


Fig. 1 Maxillary fungus ball: CT scanner (**a, d**) and MRI in T1 (**b**), T2 (**c, e**) T1 with gadolinium (**f**) in axial (**a, b, c, f**) and coronal planes (**d, e**) demonstrating a left-side maxillary sinus opacity filled with liquid (unenhanced in T1 with gadolinium, **b,**

f, arrow) containing secretions in signal void T2 (pseudo-pneumatized sinus appearance) (**b, e**, arrow) and central micro-calcification (**a, d**, arrow)

exhibit a mass-like growth pattern and variable signal intensity seen on MRI, especially in T1-weighted imaging (T1wi) due to an accumulation of mucin and fungal debris within the lesion. However, unlike neoplasm, fungus balls and mucocoeles do not enhance after gadolinium injection [13]. Therefore, T1wi after contrast injection is a reliable diagnostic tool to differentiate them from neoplasms [14]. T2wi typically reveals signal void within the lesion showing pseudo-pneumatized sinus [15] which can be responsible for misdiagnosis. This typical fungus ball imaging appearance has been described in various agents such as *A. fumigatus* [16].

Here, we report the first case of fungus ball due to *P. roqueforti*. The clinical presentation was typical in an immunocompetent middle-aged woman. As we concluded this was a noninvasive fungal sinusitis, no antifungal treatment was undertaken. Pagella et al. [2]

showed that 33.3% of their patients with fungus ball presented bone erosion. This bone erosion possibly did not implicate the fungus ball itself but rather the surrounding infection since all their patients requested only a surgical approach, and no antifungal therapy was given.

More than 65% of fungus balls are due to *Aspergillus* species, and fungal species have seldom been reported during the past decade [17]. This phenomenon could be explained by the enormous progress made in the field of fungal identification. With the development of MALDI-TOF (matrix-assisted laser desorption/ionization time of flight) mass spectrometry for fungal identification, accurate identification of fungi can be obtained in only a few minutes even if the fungal isolate does not develop typical fructification in culture [18]. Thanks to the development of the DNA amplification and

sequencing method, we were able to obtain accurate identification directly from the sinus sample without having to culture the isolate. This point is crucial since only 30% of samples are positive in culture [16]. The epidemiology of fungal sinusitis is undergoing change. Recent articles in the field report an increasing number of new fungal species associated with this medical entity: *non-fumigatus-non-flavus Aspergillus*, *Fusarium*, *Alternaria*, *Bipolaris*, *Paecylomyces*, *Scedosporium*, *Cladosporium*, *Schizophyllum* and *Penicillium* [1, 2, 19]. Regarding the *Penicillium* species, Montone et al. [1] reported that these genera represented 5% of the recovered fungi in a series of 161 fungus balls. To our knowledge, no *Penicillium* isolated from a sinus fungus ball has been identified at species level in the literature. However, a few *Penicillium* species (*Penicillium capsulatum*, *Penicillium chrysogenum*, *Penicillium piceum* and *Penicillium purpurogenum* and *Geosmithia argillacea*) have been reported to cause pulmonary mycetoma, a very similar medical entity [20–22]. *Penicillia* are seldom associated with human disease in the medical literature, with the exception of *Penicillium marneffeii*, which causes severe disseminated infection in HIV-positive patients. Few cases of invasive infections due to *Penicillium* have been reported in the literature: endocarditis, pulmonary infection, brain abscess, peritonitis, kidney infection, esophagitis [23–25].

Penicillium roqueforti has never been reported as a cause of human infection. This fungus was previously associated only with allergic pneumonitis affecting patients working in cheese manufacturing [26]. Thus, we report the first fungus ball case due to *P. roqueforti* in an immunocompetent patient.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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