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A Case of Fungus Ball-Type Pansinusitis Due to *Fusarium proliferatum*

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Abstract Incidence of fungal sinusitis due to the genus *Fusarium* has increased during the last two decades. We report a case of fungus ball sinusitis with multiple sinuses involvement in an Iranian 21-year-old woman. The patient was diagnosed as having a fungus ball-type sinusitis in computed tomography scan. The sinus biopsy revealed fungal structures on histopathological and direct microscopic examinations and a *Fusarium* species arose in culture. Partial sequencing of the translation elongation factor 1-alpha identified the isolate as *F. proliferatum*. Removal of all lesions by endoscopic surgery resulted in a favorable outcome. To the best of our knowledge, this is the first case of *F. proliferatum*-associated fungus ball which involved multi-sinus and highlights the efficiency of molecular methods for discrimination of fungal agents involved.

Keywords *Fusarium proliferatum* · Sinusitis · Fungus ball · *TEF-1α*

Introduction

The genus *Fusarium* comprises a large number of widely distributed species, of which mostly are plant parasites. Previously, it was considered as less-

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frequent fungus of clinical interest; however, presently it is known to contain emerging agents that cause a broad spectrum of infections in human, especially in patients with hematological disorders [1–4]. Fungus ball, a chronic noninvasive fungal sinusitis, often occurs in immunocompetent hosts and less frequently caused by *Fusarium* species [1, 5]. Several fungal species such as members of the genera *Aspergillus*, *Penicillium*, *Alternaria* and *Mucor* have been reported as agents of fungus ball, but the role of other fungi like *Fusarium* species was neglected [6]. Among different *Fusarium* spp., *F. solani* is the most common species implicated in human infections and *F. proliferatum* less frequently come to clinical attention [4, 7–9]. In the present study, we report the first case of fungus ball-type pansinusitis caused by *F. proliferatum* in a healthy woman from West of Iran.

Case Report

On June 2011, a 21-year-old woman, resident in Marivan, West of Iran, referred to Otolaryngology, Head and Neck Surgery department, Amir-Alam Hospital, Tehran University of Medical Sciences, Tehran, Iran, with a history of chronic headache, nasal obstruction, anosmia and mucopurulent nasal discharge for the last 3 years. No abnormalities were recorded in routine examinations, but in computed tomography (CT) scan, a diffuse polyposis with decreased bone density in the septa of ethmoidal sinuses and obstruction of ostiomeatal complex (OMC), bilaterally, were mentioned. Her past medical history was also significant for an endoscopic nasal surgery and a course of therapy with cephalexin, cefixime, cotrimoxazole and steroid nasal spray which led to almost no improvement. A biopsy was performed, and early histopathological evaluation revealed inflammatory polyposis with edematous stroma and eosinophilic infiltration, focally hyalinization and fibrosis. Afterward, the recent CT scan showed recurrence of diffuse soft tissue occupying all ethmoid, sphenoid and maxillary sinuses and OMC. The diffuse hyperdense material which filled most of these sinusal cavities made a preliminary diagnosis of fungus ball-type pansinusitis (Fig. 1). For mycological and histopathological examinations, the biopsied tissue was then subjected to pre-treatment with 15 % KOH and staining with PAS and H&E stains. In

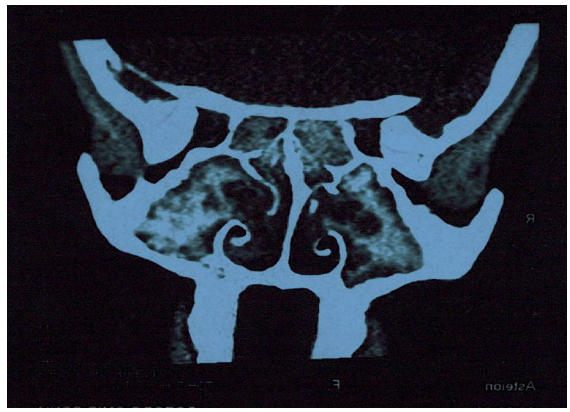

Fig. 1 Diffuse and hyperdense materials which filled most of the sinuses cavities

microscopy, hyaline, septate and typically dichotomous filaments with acute and right angles as well as some yeast-like structures (adventitious sporulation) were seen (Figs. 2a, b, 3a, b). Another portion of the tissue sample was inoculated on Sabouraud dextrose agar (Biolife, Milan, Italy) supplemented with chloramphenicol (0.5 µg/ml) and incubated at 30 °C. After 5 days, colonies with cottony surface and white color were observed, which microscopically revealed the presence of hyaline, septate, branched hyphae with sickle-shaped, multicellular macroconidia suggestive of a *Fusarium* species [10]. The patient underwent pansinus surgery aiming to remove all involved mucosa and mycelia masses. The fungal disease was eradicated, and no evidence of residual fungus ball or recurrence was detected in postoperative mycological and endoscopic follow-up, 1 year later. For more investigation, the strain was subjected to molecular identification and in vitro antifungal susceptibility testing (AFST). Genomic DNA of the isolate was extracted from colony grown on 4 % Sabouraud dextrose agar for 5 days using a conical grinder (IDEA Trading, Corp., Tokyo, Japan) as previously described method [11]. Molecular identification was accomplished using translation elongation factor 1α (*TEF-1α*). Partial amplification of the coding gene was performed using primer pairs of EF1 (5′-ATGGGTAAGGAGGACAAGAC-3′) and EF2 (5′-GGAAGTACCAGTGATCATGTT-3′) [12], under previously described cycling conditions. The amplicon was then subjected to direct sequencing on an ABI 3730XL automatic sequencer (Applied Biosystems, Foster City, USA.). The BioEdit software (http://

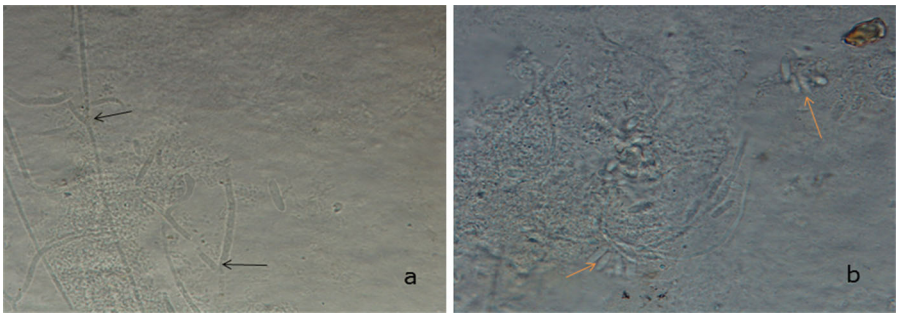

Fig. 2 KOH 10 % wet slide of sinuses discharges showing hyphae with dichotomous branching (**a**), and some yeast-like structures (**b**)

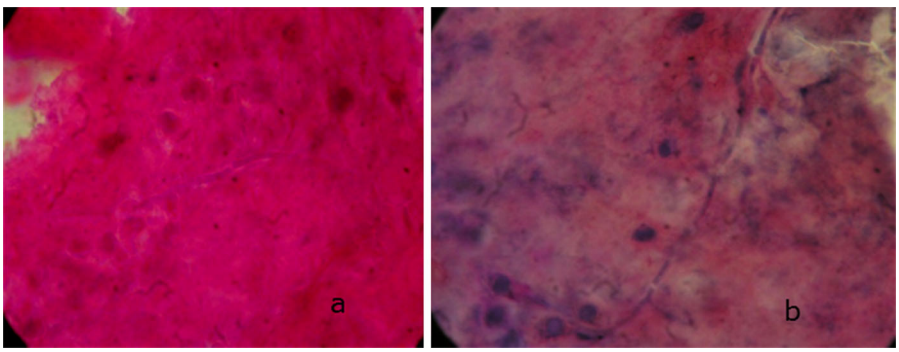

Fig. 3 PAS (**a**) and H&E (**b**) stained smears of infectious materials showing fungal elements

www.mbio.ncsu.edu/bioedit/bioedit.html) was used for sequence assembly and alignment. The obtained sequence was compared to GenBank nucleotide sequences using BLAST algorithm and showed 99.8 % identity to sequence of GenBank Accession No. JX118998 from *F. proliferatum* strain CBS 131785. The sequence was deposited in GenBank as accession JQ739146. For AFST, MICs (minimum inhibitory concentration) of strain toward eight antifungal drugs were evaluated by broth micro-dilution procedure according to the reference Clinical and Laboratory Standard Institute (CLSI) document M38-A2 [13]. *Candida krusei* (ATCC 6258), *C. parapsilosis* (ATCC 22019) and *Paecilomyces variotii* (ATCC 22319) were used for quality controls. The AFST of isolate led to MICs of 2.0, 64.0, 16.0, 2.0, 16.0 µg/ml for amphotericin B, fluconazole, itraconazole, voriconazole and posaconazole, respectively, and 8.0 µg/ml for isavuconazole, caspofungin and micafungin.

Discussion

From clinical viewpoint, in general, *Fusarium* species can cause all forms of fungal sinusitis including allergic, chronic noninvasive (fungus ball) and invasive sinusitis. Fungus balls are frequently caused by *Aspergillus* species and fusarial fungus balls, in particular, are rare [1, 14–16]. Paucity of the reports on infections by *F. proliferatum* makes it difficult to take the literature review. The species was reported from cases of onychomycosis [17], soft tissue infection [9], pneumonia [8], endophthalmitis [18], brain abscess [19] and disseminated infection [4, 7], which in many cases there were no predisposing conditions. Fungal balls occur in individuals with normal functioning immune system and usually involve a single sinus cavity, mainly the maxillary sinus. The sphenoid, ethmoid or frontal sinuses may involve less commonly [20]. To the extent of our knowledge, there is just one report on fungal ball-type sinusitis with multiple sinuses involvement that was caused by *Schizophyllum commune* [6]. But pansinus involvement due to *F. proliferatum* has not been documented, and *F. proliferatum* is an uncommon agent of fungal sinusitis among *Fusarium* species [14, 16]. As a whole, the definite process by which a fungus ball forms is unknown but overfilling of maxillary cavities during endodontic treatment of maxillary molar was

proposed as a nidus for development [20]. It was also narrated as a secondary condition due to a chronic sinusitis, and in most cases of recurrent sinusitis, nasal endoscopy was shown leading to extension of infection from the nose into the larger sinuses [14]. On the other hand, OMC obstruction, as seen in our case, was found to have no correlation with the growth of maxillary fungus ball which disproves these hypotheses [21]. In the case of our patient, she had never had a dental procedure and seemingly the last nasal endoscopic surgery led to development of the infection as a pansinusitis fungus ball. Due to unknown reasons, and as seen in our patient, fungal balls more commonly occur in middle- or older-age females [20, 22]. The diagnosis of fusariosis is mainly based on histopathological and mycological findings [10]. From diagnostic standpoint, *Fusarium* species are known to develop dichotomous hyaline filaments with acute and right angles in tissues similar to those of *Aspergillus* species. But as observed in our case (Fig. 2a, b), *Fusarium* spp. have the ability to sporulate in tissues and develop specific reproductive yeast-like conidia in a phenomenon known as "adventitious sporulation." These diagnostic clues are helpful to distinguish *Fusarium* infections from other saprobes [23]. The definite diagnosis, which is of epidemiological and medical importance, needs the isolation of *Fusarium* spp. from clinical samples. *Fusaria* can morphologically be identified via the production of hyaline, banana-shaped, long and multiseptate macroconidia at the genus level [10], but delineation down to the species level is difficult and may require sequencing of translation elongation factor 1-alpha (*TEF-1α*) as golden standard [24], and in this regard, partial sequencing of *TEF-1α* enabled us to identify our isolate as *F. proliferatum*. From therapeutic point of view, since there is no effective medical therapy, some clinicians recommend endonasal removal of all lesions by endoscopic approaches as definitive treatment of choice for fungus ball [14, 25]. However, it is logical to consider AFST pattern in fungal sinusitis, especially in cases of recurrence or infection due to uncommon species. Albeit different in AFST patterns, *Fusarium* species are highly refractory to the most antifungal agents [1]. Our *F. proliferatum* isolate was almost resistant to all tested antifungals in vitro, but fortunately, the patient recovered after functional endoscopic sinus surgery (FESS). The presented case has greatly extended our knowledge on the causatives of fungal pansinusitis to consider *F. proliferatum* as a new potential agent. It also reconfirms this view that early mycological and molecular recognition can help the accurate treatment of a fungal infection.

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Conflict of interest None.

References

1. Nucci M, Anaissie E. *Fusarium* infections in immunocompromised patients. Clin Microbiol Rev. 2007;20:695–704.
2. Dananché C, Cassier P, Sautour M, et al. Fungaemia caused by *Fusarium proliferatum* in a patient without definite immunodeficiency. Mycopathologia. 2014 [Epub ahead of print].
3. Nucci M, Anaissie EJ, Queiroz-Telles F, et al. Outcome predictors of 84 patients with hematologic malignancies and *Fusarium* infection. Cancer. 2003;98:315–9.
4. Summerbell RC, Richardson SE, Kane J. *Fusarium proliferatum* as an agent of disseminated infection in an immunosuppressed patient. J Clin Microbiol. 1988;26(1):82–7.
5. Wickern GM. *Fusarium* allergic fungal sinusitis. J Allergy Clin Immunol. 1993;92:624.
6. Nazeri M, Mohammadi Ardehali M, Moazeni M, et al. A case of fungus ball type pansinusitis caused by *Schizophyllum commune*. Med Mycol Case Rep. 2012;1:115–8.
7. Helm TN, Longworth DL, Hall GS, Bolwell BJ, Fernandez B, Tomecki KJ. Case report and review of resolved fusariosis. J Am Acad Dermatol. 1990;23:393–8.
8. Herbrecht R, Kessler R, Kravanja C, Meyer MH, Waller J, Letscher-Bru V. Successful treatment of *Fusarium proliferatum* pneumonia with posaconazole in a lung transplant recipient. J Heart Lung Transplant. 2004;23:1451–4.
9. Palmore TN, Shea YR, Childs RW, Sherry RM, Walsh TJ. *Fusarium proliferatum* soft tissue infection at the site of a puncture by a plant: recovery, isolation, and direct molecular identification. J Clin Microbiol. 2010;48:338–42.
10. Anaissie EJ, McGinnis MR, Pfaller MA. Clinical mycology. Philadelphia: Elsevier Science; 2009. p. 313–7.
11. Abastabar M, Mirhendi H, Rezaei-Matehkolaei A, Shidfar MR, Kordbacheh P, Makimura K. Restriction analysis of β-Tubulin genefor differentiation of the common pathogenic dermatophytes. J Clin Lab Anal. 2014;28:91–6.
12. O'Donnell K, Kistler HC, Cigelnik E, Ploetz RC. Multiple evolutionary origins of the fungus causing Panama disease of banana: concordant evidence from nuclear and mitochondrial gene genealogies. Proc Natl Acad Sci USA. 1998;95:2044–9.
13. Clinical and Laboratory Standards Institute. Reference method for broth dilution antifungal susceptibility testing of filamentous fungi. CLSI Document M38-A2, Wayne, PA 2008.

14. Stammberger H. Endoscopic surgery for mycotic and chronic recurring sinusitis. Ann Otol Rhinol Laryngol Suppl. 1985;119:1–11.
15. Chakrabarti A, Das A, Panda NK. Overview of fungal rhinosinusitis. Indian J Otolaryngol Head Neck Surg. 2004;56:251–8.
16. Kurien M, Anandi V, Raman R, Brahmadathan KN. Maxillary sinus fusariosis in immunocompetent hosts. J Laryngol Otol. 1992;106:733–6.
17. Hattori N, Shirai A, Sugiura Y, et al. Onychomycosis caused by *Fusarium proliferatum*. Br J Dermatol. 2005;153(3): 647–9.
18. Ferrer C, Alio J, Rodriguez A, Andreu M, Colom F. Endophthalmitis caused by *Fusarium proliferatum*. J Clin Microbiol. 2005;43:5372–5.
19. Peterson A, Pham MH, Lee B, et al. Intracranial fusarium fungal abscess in an immunocompetent patient: case report and review of the literature. J Neurol Surg Rep. 2014; 75:e241–5.
20. Soler ZM, Schlosser RJ. The role of fungi in diseases of the nose and sinuses. Am J Rhinol Allergy. 2012;26:351–8.
21. Tsai TL, Guo YC, Ho CY, Lin CZ. The role of ostiomeatal complex obstruction in maxillary fungus ball. Otolaryngol Head Neck Surg. 2006;134:494–8.
22. Nomura K, Asaka D, Nakayama T, et al. Sinus Fungus Ball in the Japanese population: clinical and imaging characteristics of 104 cases. Int J Otolaryngol. 2013;2013:731640.
23. Liu K, Howell DN, Perfect JR, Schell WA. Morphologic criteria for the preliminary identification of *Fusarium*, *Paecilomyces*, and *Acremonium* species by histopathology. Am J Clin Pathol. 1998;109:45–54.
24. O'Donnell K, Sutton DA, Rinaldi MG, et al. Internet-accessible DNA sequence database for identifying *Fusaria* from human and animal infections. J Clin Microbiol. 2010;48:3708–18.
25. Netkovski J, Shirgoska B. Fungal rhinosinusitis. Prilozi. 2012;33:187–91.