

CASE REPORT

Allergic Fungal Sinusitis Caused by *Exserohilum rostratum* and Literature Review

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Abstract A case of allergic fungal sinusitis (AFS) caused by *Exserohilum rostratum*, proven by culture and histopathology of the biopsy material, is described. The identity of the isolate was confirmed by sequencing of ITS region of rDNA. To the best of our knowledge, this is the first report of allergic *E. rostratum* sinusitis from Kuwait and Arabian Peninsula. Ten previously described cases of AFS have been reviewed. The report highlights the emerging importance of *E. rostratum* as a human pathogen in this region and role of molecular methods in its accurate identification.

Keywords *Exserohilum rostratum* · Fungal sinusitis · Molecular diagnosis

Introduction

The members of the genus *Exserohilum* (Pleosporales, Ascomycota) are environmental fungi that are ubiquitous in nature. They are mainly prevalent in warm tropical and subtropical regions of the world [1]. Of nearly 25 species included in the genus, only three, namely *E. rostratum*, *E. longirostratum* and *E. mcginnisii*, are known to be pathogenic for humans [2]. Recent taxonomic and molecular studies have revealed considerable homology between these three species, suggesting that they may represent a single species [2, 3]. *Exserohilum* species are capable of causing cutaneous, corneal and systemic infections [1]. Most of the cases have been reported in patients with a history of immunosuppression, trauma and in atopic individuals [1, 4]. Here, we describe a case of allergic fungal sinusitis (AFS) caused by *E. rostratum* in a young boy with a history of bronchial asthma who presented with recurrent episodes of sinusitis. The diagnosis was made by direct microscopy and culture of the sinus material. The isolate was identified by phenotypic characteristics and sequencing of ribosomal DNA (rDNA).

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Case Report

A 16-year-old Kuwaiti male, a known case of bronchial asthma and recurrent fungal sinusitis, reported to an outpatient department (OPD) in Ear, Nose and Throat Unit (ENT) of Adan Hospital on February 2016, complaining of left frontal headache with nasal obstruction. On examination, there was severe deviated nasal septum to right and presence of left nasal polyposis. CT scan showed mucosal thickening in the left sinuses and right sphenoid sinus. The patient was admitted for functional endoscopic sinus surgery (FESS) in February, 2016, and all nasal polyps and the fungal mass were removed and cleaned. The patient was discharged after 2 days and was followed-up in Outpatient Department for 1 month. Few months later, the patient came back again to ENT OPD with recurrent nasal obstruction, headache and left eye proptosis. CT scan of sinuses performed at this time showed thickening of mucosa of the left nasal sinuses, right sphenoid sinus and right frontal sinus with erosion of the roof of left orbit and septum between the two frontal sinuses as well as erosion of septum between two sphenoid sinuses (Fig. 1). The patient was admitted again, and FESS along with septoplasty was performed in January, 2017. The fungal mass was

removed from all sinuses (Fig. 2). Additionally, oculoplastic surgeon removed the fungus from the orbit with closure of the orbital defect with Midpore. The patient was discharged after 2 days but continued to be followed-up in OPD for 1 year with no recurrence (Fig. 2). The patient was prescribed short courses of oral prednisolone for varying periods (4–8 weeks) for the management of asthma. No antifungal therapy was administered.

The allergic nature of sinusitis was supported by histopathological examination of the resected polypoid mass which revealed mixed inflammatory cellular response with predominance of eosinophils and Charcot-Leyden crystals. Gomori-methenamine-silver (GMS)-stained sections showed presence of fungal elements. Few foci showed evidence of bony erosion. The resected nasal material was received in Mycology Reference Laboratory, Department of Microbiology, Faculty of Medicine under routine patient care for culture, identification of the isolate and antifungal susceptibility testing. Calcofluor-KOH preparation of the nasal material showed septate hyphal elements, some with bulging structures (Fig. 3). The culture of the resected mass yielded a pigmented fungus.

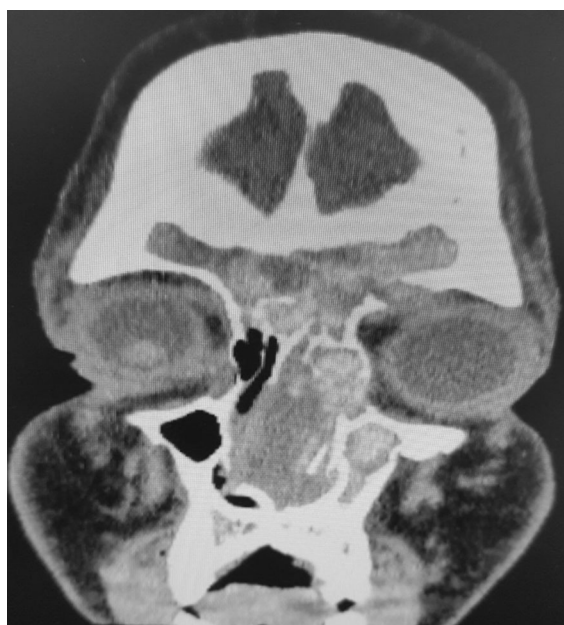


Fig. 1 CT scan done on 19/12/2016 preoperative showing fungal sinusitis mainly left side with erosion of the roof of orbit and extension to the left eye

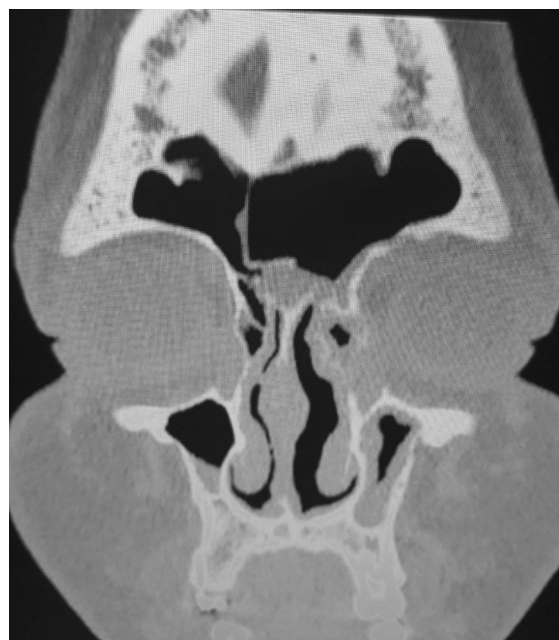


Fig. 2 CT done on 26/4/2017 postoperative after 4 months with good aeration to the sinuses

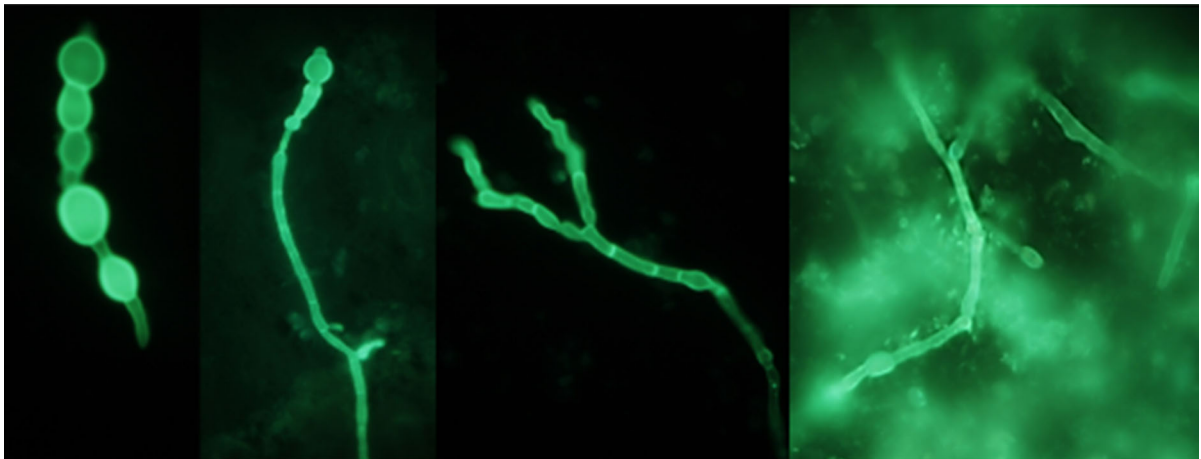


Fig. 3 Potassium hydroxide–calcofluor preparation from nasal tissue material showing varied morphological forms of *E. rostratum*, magnification $\times 400$

Phenotypic and Molecular Identification

The isolate grew rapidly on Sabouraud dextrose agar supplemented with chloramphenicol giving a dark gray appearance with cottony texture. Microscopically, the isolate showed melanized septate hyphae producing long brown-colored fusiform shaped conidia, measuring 30–80 μm in size. These conidia were thick-walled with 5–10 septa and showed a protruding hilum. Distinctive dark septum was observed at each end of the mature conidia (Fig. 4). For molecular identification, genomic DNA was obtained from the isolate (Kw337/16) as described previously [5]. The internally transcribed spacer (ITS) region of rDNA was amplified and sequenced as described previously [6]. The isolates exhibited complete sequence identity with two strains (FMR 11399 and 11328) and one nucleotide difference with *Exserohilum rostratum* CBS 112815. The ITS region sequence has been deposited in the GenBank (accession no. LT984841).

Antifungal Susceptibility of the Isolate by Etest

Etest was performed according to the manufacturer's instructions by using RPMI 1640 medium supplemented with 2% dextrose as described previously [7]. Briefly, each 150-mm petri plate contained 60 ml of solidified medium. After culturing the isolates onto potato dextrose agar slants (Remel) at 30 °C for 5 days, the conidia were harvested in 2 ml sterile

normal saline and clumps were allowed to settle. The conidial suspension was adjusted to a concentration of 10^6 spores/ml and was liberally spread over the surface of the medium. The plates were allowed to dry for 15 min before applying the Etest strips (bioMérieux, Marcy l'Etoile, France). Plates were incubated at 35 °C, and minimum inhibitory concentrations (MICs) were determined after 24 h of incubation. The Etest MICs were read at the lowest drug concentration at which the border of the zone of inhibition intercepted the scale on the antifungal strip. The MICs for itraconazole, voriconazole, amphotericin B and caspofungin were as follows: 0.016, 0.016, 0.023 and 0.094 $\mu\text{g/ml}$, respectively.

Discussion

The present report is noteworthy as it describes a rare case of AFS caused by *E. rostratum*. The identity of the isolate was unequivocally established by sequencing of ITS region of rDNA. Additionally, the presence of nasal polyposis, long history of bronchial asthma/atopy and abundance of eosinophils and Charcot-Leyden crystals in the mucinous material supported the diagnosis of AFS in our patient. Consistent with the current surgical approach for the management of AFS, our patient was successfully managed by endoscopic sinus surgery that was aimed to relieve the obstruction by removing mucin, debris and fungal elements to improve ventilation and to reduce

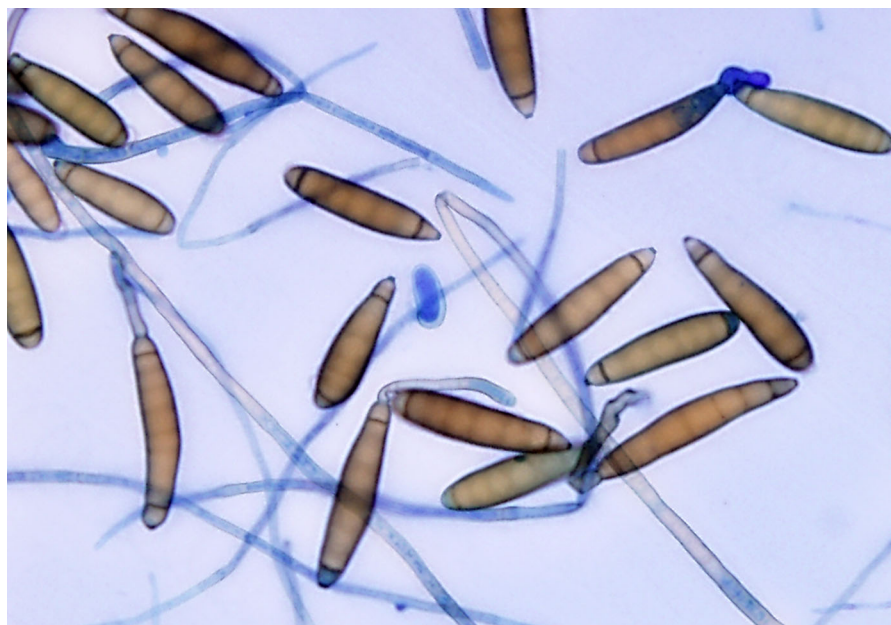


Fig. 4 Lacto-phenol cotton blue mount of showing brown-colored multiseptate conidia of *E. rostratum* characterized by the protruding hilum and distinctive dark septa at each end of the conidia, magnification $\times 400$

antigenic stimulus. To the best of our knowledge, this is the first report of AFS caused by *E. rostratum* from Kuwait and the Arabian Peninsula. So far, 10 cases of culture-proven AFS due to *Exserohilum* sinusitis have been reported. The salient findings in these cases are summarized in Table 1 [8–14]. All the patients had allergic predisposition which manifested as allergic rhinitis, bronchial asthma or nasal polyps and responded to surgical interventions with or without antifungal or steroid therapy.

In the absence of species-specific identification of fungal isolates, diagnosis of AFS in most of the early reports was based on characteristic clinical, radiological and histopathological findings. Although *E. rostratum* is the most pathogenic species within the genus, it has rarely been recognized as a cause of AFS [1, 4]. Early reports implicating *Exserohilum* species in AFS were described from the USA [8, 9]. In a study from Mayo clinic, USA, none of the 37 cases of AFS yielded *Exserohilum* in culture [15]. Torres et al. [14] described 16 cases of AFS from Anderson Cancer Center, Houston, USA, and *Exserohilum* species was grown in culture from three cases. These authors also reviewed 150 cases of AFS, 81% of the isolates represented dematiaceous fungi, and *Exserohilum* species were responsible for only 6% of the cases

[14]. In general, dematiaceous fungi (particularly *Bipolaris*) cause greater proportion of cases of fungal sinusitis than *Aspergillus* species in the USA [13], whereas in the Middle East and India, *Aspergillus* species, particularly *A. flavus*, is the preponderant species associated with AFS. Although AFS is a global disease [16], it has a relatively higher incidence in areas with dry and warm climate, such as Saudi Arabia, Sudan, Qatar and North India [17–19]. The same also applies to AFS cases reported from South-western states of the USA, such as Arizona and Texas [8, 20].

Exserohilum species are capable of causing a wide spectrum of clinical manifestations including systemic, cutaneous and sinus infections [1, 4]. The first case of AFS by *Exserohilum* species from the Middle East was described in a 15-year-old healthy boy from Israel who was treated by surgery, amphotericin B and prednisone [10]. The rarity of reports of sinusitis due to *Exserohilum* species may be attributed to lack of expertise in phenotypic identification of dematiaceous fungi. It is possible that some of the *Exserohilum* isolates might have been misidentified as *Bipolaris* species.

The first case of invasive *Exserohilum* infection was reported in 1986 in a 34-year-old female who

Table 1 Summary of cases of chronic allergic fungal sinusitis caused by *Exserohilum* species

References, year	Age/sex	Country	<i>Exserohilum</i> species	Presentation/ underlying condition	Radiological findings	Management	Outcome
Padhey et al. [8]	27/M	Arizona, USA	<i>E. mcginnisii</i>	Allergies, 6-year history of nasal polyps	Polyps in maxillary, sphenoid and ethmoid sinuses	Surgery (Bilateral Caldwell-Luc operation)	Improved
Adam et al. [9]	10/M	Arizona, USA	<i>E. rostratum</i>	Allergic rhinitis	Bilateral nasal polyps, opacification of left maxillary sinus, extension to left ethmoid sinus	Surgery, AMB; 6 weeks	Cured
Adam et al. [9]	25/M	Arizona, USA	<i>Exserohilum</i> species	Nasal polyps	Bilateral ethmoid, sphenoid and frontal sinus opacification	Multiple surgical debridement	Cured
Aviv et al. [11]	19/M	New York, USA	<i>E. rostratum</i>	Nasal polyps	Bilateral ethmoid, frontal, sphenoid and nasal sinuses	Surgery	Cured
Friedman et al. [12]	11/M	Texas, USA	<i>Exserohilum</i> species	Bronchial asthma	Soft tissue mass in rt. Nasal cavity, maxillary, ethmoid and sphenoid sinuses	Surgery, ketoconazole	Cured
Manning et al. [13]	31/M	Texas, USA	<i>Exserohilum</i> species	Allergy, sinusitis	Involvement of multiple sinuses	Surgery, (endoscopic drainage)	Cured, 7 months
Torress et al. [14]	14/M	Texas, USA	<i>Exserohilum</i> species	Atopy, wheezing, decreased left eye vision	Soft tissue mass involving multiple sinuses, bone erosion	Surgery	NED, 2 months
Torress et al. [14]	34/F	Texas, USA	<i>Exserohilum</i> species	Nasal congestion, recurrent L hypoesthesia and diplopia	Soft tissue masses, bilateral maxillary, ethmoid and sphenoid sinuses, destruction of clivus with intracranial extension	Surgery	NED, 5 months
Torress et al. [14]	11/M	Texas, USA	<i>Exserohilum</i> species	Bronchial asthma, periorbital swelling, rt. proptosis	Soft tissue masses, Rt. nasal cavity, Rt. Maxillary, ethmoid and sphenoid sinuses, bone erosion	Surgery	NED, 8 months
Colton et al. [10]	15/M	Israel	<i>E. rostratum</i>	Mild allergy	Rt. Naso-ethmoidal mass with bony erosion, destruction of nasal turbinates and septum	Surgery, AMB (12 days)	Cured, discharged on prednisolone
Present case	16/M	Kuwait	<i>E. rostratum</i>	Left frontal headache with nasal obstruction	Nasal sinuses and right sphenoid sinus with bone erosion	Surgery	Improved

AMB Amphotericin B, NED no evidence of disease

underwent cardiac transplantation in 1975 in the USA [21]. Culture of biopsies obtained from subcutaneous nodules present on her right leg yielded a dematiaceous mold, identified as *E. rostratum*. A recent review of 48 cases of *Exserohilum* infections revealed that 60.4% infections were caused by *E. rostratum* alone and 73% of 48 cases had systemic infection [4]. It was noted that sinus involvement was the most common clinical manifestation (48%) in these cases and 12.5% of the cases were atopic. It seems that *E. rostratum* has some level of propensity to infect sinuses in atopic and immunocompromised individuals [22, 23]. Here, attention may also be drawn to an outbreak of meningitis among 750 cases that occurred following injections of methylprednisolone that was contaminated with this fungus and resulted in 61 deaths [24, 25]. The diversity of clinical manifestations observed in these patients prompted investigators to undertake in-depth studies to understand virulence attributes of this fungus that contribute to its pathogenicity [26–28]. This outbreak illustrated that under favorable conditions an organism that normally has low pathogenic potential for humans can transform into a very dangerous pathogen.

Like our isolate, amphotericin B and some other azoles possessed good in vitro activity against *Exserohilum* species, although there are considerable inter-strain variations in susceptibility to different antifungal agents [29]. While both environmental and clinical isolates are capable of causing human infections [27, 30], there are inter-strain differences, possibly suggesting existence of cryptic species in *E. rostratum* [28]. In most of the published case studies requiring systemic antifungal therapy, amphotericin B alone or in combination with one of the triazoles has been used as a therapeutic option. Surgical approach has been mainly used for debridement of infected tissue from cases which had cutaneous or sinus infection and may be combined with antifungal therapy [4]. Currently, there is a lack of strong evidence to recommend routine oral or topical use of antifungal agents for the treatment of AFS. There is a need to conduct well-designed, prospective studies to assess the benefit of antifungal therapy in the management of AFS [16]. Similar to our patient, surgery and oral steroids have also been used postoperatively for reducing recurrence and inflammatory response, thus improving the outcome and may even be obviating the need of repeated surgical interventions [31]. However, due to limited

number of documented cases of *Exserohilum* sinusitis, the experience in the management of these cases is restricted to few reports [8–14]. Our patient was managed with repeated use of steroids with no recurrence. Recent studies have shown that *E. rostratum* possesses receptors for corticosteroids which possibly promote its growth [26, 32]. It is, therefore, a moot point whether steroids should be used for the management of *Exserohilum* sinusitis. A better understanding of the effect of corticosteroids on growth, virulence and melanization of *E. rostratum* is required to avoid any possible therapeutic implications. It has been reported that dematiaceous fungi are present on the top layers of the desert soil/sand and thus can easily become airborne [33]. *E. rostratum* is a cross-Kingdom pathogen capable of infecting humans as well as plants, which could have provided the source of infection in our patient [30].

The limitations of our study are that no skin testing was performed in our patient to demonstrate type 1 hypersensitivity and total/specific immunoglobulin E levels were also not determined.

In conclusion, we have described a case of AFS caused by *E. rostratum* proven by culture and histopathology of the biopsy material. The identity of the isolate was confirmed by sequencing of ITS region of rDNA. To the best of our knowledge, this is the first report of allergic *E. rostratum* sinusitis from Kuwait and the Arabian Peninsula. Since *Exserohilum* species have close morphological similarities with *Bipolaris* species, a better understanding of characteristic morphological features and application of molecular methods can help in specific identification.

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Compliance with Ethical Standards

Conflict of interest Authors declare no conflict of interest.

Ethical Statement The patient's informed consent was obtained to publish this report.

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