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Case report

Management of frontal sinus fungal osteomyelitis in the COVID 19 era: A case series[☆]Hisham Atef Ebada^{*}, Ahmed MUSAAD Abd El-Fattah, Ali Tawfik

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ABSTRACT

The aim of this study was to review different approaches and outcomes in the management of post-COVID-19 frontal sinus fungal osteomyelitis.

The study included 19 patients with frontal sinus fungal osteomyelitis. The main line of treatment was surgical debridement (sequestrectomy). Approaches included combined external and endoscopic approaches (n = 15) and pure endoscopic approaches (n = 4) according to the extent and accessibility of the sequestrum. Postoperative healing was satisfactory in all patients. All patients returned to their normal daily activity within 4–6 weeks, without residual or recurrent frontal sinus infection, osteomyelitis or need for revision procedures.

Within the limitation of this case series, it seems that there is no need to adopt a new therapy regimen for treatment of frontal sinus fungal osteomyelitis because the conventional and well-known treatment approach combining surgery and antifungal drugs seems to work well. However, early, and adequate debridement and sequestrectomy is crucial. Furthermore, an open approach may be required according to the extent of osteomyelitis.

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1. Introduction

Post-COVID-19 invasive fungal sinusitis (IFS) is a new clinical entity that has been recently described by some authors (El-Kholy et al., 2021; Mekonnen et al., 2021; Sebastian et al., 2021). A sharp increase in the incidence of IFS was noticed in post-COVID-19 patients than in those of non-COVID-19 (Ismail et al., 2021). Given the robust inflammation and concurrent immunosuppression evident in COVID-19, it is believed that the dysregulated immune response provides a hospitable environment for the development of fungal co-infections (Gangneux et al., 2020). Furthermore, there are shared risk factors for COVID-19 and IFS, including pre-existing immunosuppression and comorbidities such as diabetes mellitus (Erener, 2020). In addition, it is important to consider that the use of corticosteroids which are prescribed for COVID-19 related complications may potentially reduce immune response (Lai and Yu,

2020). IFS is characterized by fungal invasion of the mucosa of the paranasal sinuses and destruction of the adjacent structures through angioinvasion (Wandell et al., 2018). It is usually caused by *Aspergillus* or *Mucor* (Cho et al., 2015; Nyunt et al., 2021).

Frontal sinus osteomyelitis (FSO) occurs most commonly due to complicated acute or chronic rhinosinusitis, trauma or as a complication of surgical obliteration of the frontal sinus (Thompson et al., 2021; Raponi et al., 2021). Fungal osteomyelitis may occur in the frontal sinus in a setting of invasive fungal sinusitis, as a result of vascular invasion and bone necrosis (Srivastava et al., 2019). Fungal osteomyelitis of the frontal sinus is very rare (Verma et al., 2013). Post-COVID-19 fungal osteomyelitis in the maxillofacial region has been reported recently (Verma and Bali, 2021; Suresh et al., 2022; Said et al., 2021; Shirke and Chitguppi, 2021), however, the main sites affected in these reports were in the maxilla and mandible.

Osteomyelitis is characterized by bony destruction and sequestrum formation (Bhanwala et al., 2021). The frontal sinus is closely related to the orbit and skull base, making the potential complications of infection more serious and fatal (Chaturvedil et al., 2004). FSO typically presents with fever, headache, nasal discharge, forehead swelling, photophobia, orbital pain, and periorbital edema

[☆] This study was conducted in the Otorhinolaryngology Department, Faculty of Medicine, Mansoura University, Egypt.

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(Chaturvedil et al., 2004; Deutsch et al., 2000; Al-Qudah and Graham, 2012). It can also manifest as a draining cutaneous fistula (Chaturvedil et al., 2004; Jaswal et al., 2007).

Early diagnosis and immediate intervention are crucial for fungal FSO. There is a paucity of literature regarding the optimum management paradigms for FSO in the age of advanced endoscopic techniques. Treatment modalities include surgical debridement (sequestrectomy), treatment of the underlying immune suppression, and antifungal drugs (Srivastava et al., 2019). This study was conducted to review different approaches and outcomes in the management of post-COVID-19 frontal sinus fungal osteomyelitis.

2. Case series

This retrospective study was conducted in the Otorhinolaryngology Department, Faculty of Medicine, Mansoura University, Egypt, over the last one year (June 2020–June 2021). The study was approved by the Mansoura Faculty of Medicine Institutional Research Board (MFM-IRB: R.21.11.1524). A review of the database of patients with post-COVID-19 invasive fungal sinusitis revealed 19 patients with frontal sinus osteomyelitis. This study included 9 males and 10 females. Patients' ages ranged from 39 to 72 years with a mean of 57 years. Table 1 shows the demographic, clinical and surgical data of the patients.

All patients had post-COVID-19 IFS. The interval between the diagnosis of COVID-19 and IFS ranged from 14 to 40 days (mean: 21.6). Diagnosis and management of COVID-19 was made according to the most recent national management protocol (Ministry of Health and Population, Egypt. version 1.5/September 2021) (Masoud et al., 2021). Diagnosis of COVID was proved by PCR and chest CT findings. Five out of 19 patients were diagnosed as mild COVID-19 and were not hospitalized. On the other hand, 10 patients had moderate COVID-19, and 4 patients had severe COVID-19. Two patients with severe infection needed invasive mechanical ventilation. Patients with moderate and severe infection were hospitalized either in the COVID-19 isolation unit in the Mansoura University Hospitals (n = 6) or in other centers (n = 8). The main lines of treatment for COVID-19 were antiviral drugs (n = 17), systemic steroids (n = 16), anticoagulants (n = 11), along with symptomatic treatments and multivitamins.

Diagnosis and management of invasive fungal sinusitis was made according to the Global guideline for the diagnosis and management of Mucormycosis (2019), (Cornely et al., 2019). Diagnosis was made based on endoscopic endonasal findings of mucosal pallor, blackening, gangrene, and/or palatal ischemia, gangrene, and/or orbital proptosis, ophthalmoplegia, or vision loss. FSO was diagnosed by CT scan with mottled, moth-eaten appearance of the affected bone with sequestrum formation (Fig. 1). In the

Table 1
Patients' data.

No.	Age	Gender	Interval between COVID and IFS In days	Presentation	Extent of disease	Previous endoscopic debridement for IFS	Treatment approach	Fungus Type
1	62	Male	14	Forehead swelling, frontal headache	Bilateral Frontal sinus	Yes	Bicoronal approach, with Draf III	Mucor
2	45	Female	21	Headache	Unilateral Frontal sinus	Yes	Eye-brow incision, with Draf II	Mucor
3	59	Female	40	Forehead swelling, nasal obstruction, discharge	Bilateral frontal sinus, ethmoid, maxillary.	No	Bicoronal approach, with Draf III, endoscopic debridement for nose and other sinuses	Mucor
4	72	Female	15	Headache, nasal obstruction	Unilateral frontal sinus, ethmoid, nasal septum	No	Endoscopic Draf II, endoscopic debridement for nose and other sinuses	Mucor
5	39	Male	18	Nasal discharge	Unilateral frontal sinus, ethmoid	No	Eye-brow incision, with Draf II	Mucor
6	52	Female	31	Frontal headache, proptosis, loss of vision	Unilateral frontal sinus, ethmoid, maxillary, orbital	No	Bicoronal approach, with Draf II, endoscopic debridement for nose and other sinuses, orbital decompression	Mucor
7	60	Female	20	Nasal burning, discharge, epistaxis	Unilateral frontal sinus, ethmoid, nasal septum	No	Bicoronal approach, with Draf II, endoscopic debridement for nose and other sinuses	Mucor
8	67	Male	14	Headache, anosmia	Bilateral frontal sinus	No	Endoscopic Draf III	Mucor
9	48	Male	29	Nasal obstruction, headache	Bilateral frontal sinus	Yes	Bicoronal approach, with Draf III	Mucor
10	50	Female	18	Nasal obstruction, headache	Unilateral frontal sinus, ethmoid, maxillary, sphenoid, nasal septum	No	Bicoronal approach, with Draf II, endoscopic debridement for nose and other sinuses	Mucor
11	66	Male	21	Nasal obstruction, loose teeth	Bilateral frontal sinus, ethmoid, maxillary, nasal septum, palate	No	Bicoronal approach, with Draf III, endoscopic debridement for nose and other sinuses, and palate	Mucor
12	52	Female	17	Nasal obstruction, headache, proptosis	Bilateral frontal sinus, orbit	No	Forehead incision, with Draf III, orbital exenteration	Mucor
13	58	Female	29	Nasal obstruction, discharge, loss of vision, proptosis, ophthalmoplegia	Bilateral frontal sinus, ethmoid, nasal septum, orbit	No	Bicoronal approach, with Draf III, endoscopic debridement for nose and other sinuses, orbital decompression	Mucor and Aspergillus
14	45	Male	15	Headache	Unilateral frontal sinus	Yes	Endoscopic with Draf II	Mucor
15	60	Female	19	Forehead draining sinus	Unilateral frontal sinus	Yes	Bicoronal approach, with Draf II	Mucor
16	70	Male	23	Headache, nasal obstruction	Bilateral frontal sinus, ethmoid	Yes	Bicoronal approach, with Draf III, endoscopic debridement for nose and ethmoid	Mucor
17	68	Male	31	Loss of vision, ophthalmoplegia	Unilateral frontal sinus, ethmoid, maxillary, nasal septum, orbit	No	Endoscopic Draf II, endoscopic debridement for nose and other sinuses, orbital decompression	Aspergillus
18	51	Male	15	Forehead swelling, headache	Bilateral frontal sinus.	No	Bicoronal approach, with Draf III	Mucor
19	58	Female	20	Nasal obstruction, headache, loose teeth, palatal ulcer	Unilateral frontal sinus, ethmoid, maxillary, sphenoid, nasal septum, palate	No	Bicoronal approach, with Draf II, endoscopic debridement for nose and other sinuses, and palate	Mucor

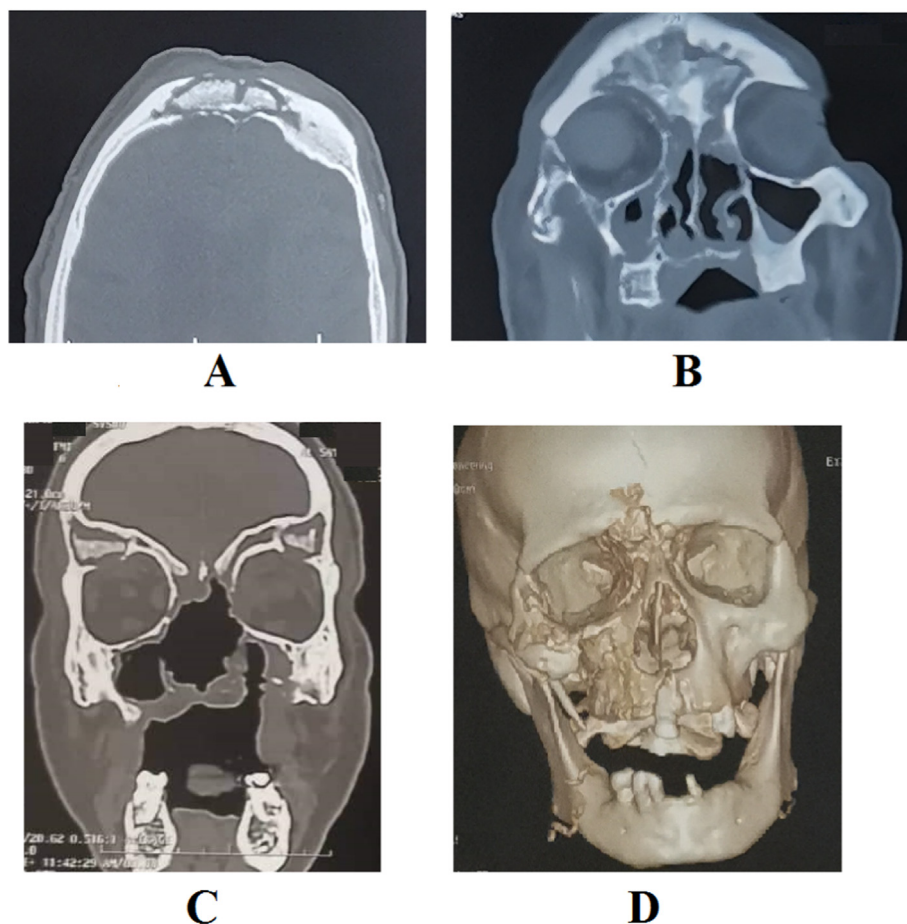


Fig. 1. CT scans showing frontal sinus fungal osteomyelitis (FSO). A: Axial CT. B: coronal CT of another patient with FSO associated with right maxillary and zygomatic osteomyelitis. C: Another patient with bilateral FSO, with history of endonasal debridement of invasive fungal sinusitis. D: Three dimensional CT showing FSO with zygomatic and maxillary osteomyelitis.

CT scan, osteomyelitis can be differentiated from fungus ball in the paranasal sinus. The hyperdensity of the fungus ball is usually less dense than bone, and sinus walls show expansion rather than erosion.

Presenting symptoms were headache ($n = 12$), nasal obstruction and/or discharge ($n = 11$), orbital manifestations (proptosis and/or vision loss and/or ophthalmoplegia) ($n = 4$), forehead swelling ($n = 3$), loose teeth ($n = 2$), draining forehead sinus ($n = 1$) and anosmia ($n = 1$). The FSO was unilateral in 10 patients and bilateral in 9 patients. Six patients in the study had undergone previous endoscopic endonasal debridement for IFS in other centers and were referred for further management of FSO.

Sixteen patients had insulin-dependent diabetes mellitus. Three out of those 16 patients were diagnosed as new-onset diabetes, concomitant with COVID-19. New-onset diabetes may be triggered or aggravated by the COVID-19 infection or the systemic steroid therapy. Other comorbidities were reported in the form of liver disease ($n = 2$), renal impairment ($n = 1$). No other infectious diseases were reported in this study. Eighteen patients were dentate, and the remaining 1 was edentulous. The socioeconomic status of the patients was high in 5 patients, middle in 8, and low in 6. Twelve patients were rural, and 7 patients were urban. There was no significant difference between patients regarding educational qualifications, cultural and occupational factors.

Immediate treatment of IFS (surgical debridement, sequestrectomy and empirical antifungal drugs) was initiated upon

clinical diagnosis without waiting for pathology or culture results as the delay in treatment is associated with high morbidity and mortality. Surgeries were performed in the Otorhinolaryngology department, Mansoura University Hospitals for all patients ($n = 19$). In 17 out of 19 patients, nasopharyngeal swabs for COVID-19 were negative at the time of diagnosis of FSO, while in the remaining 2 patients, swabs were positive. In these 2 patients, antifungal treatment was started, and surgery was delayed until obtaining two consecutive negative nasopharyngeal swabs. The delay was 7 days in one patient and 10 days in the other one.

Regarding FSO, surgical treatment was the main line with the aim of complete sequestrectomy and debridement of necrotic tissue, as well as achieving long term frontal sinus patency. Combined approaches (open and endoscopic) were performed for 15 out of 19 patients in the study. In this group of patients, complete removal of the sequestrum was not possible with the endoscopic approach due to the large size and the location of the sequestrum laterally within the frontal sinus. Open approaches included bicoronal approach ($n = 11$), direct eyebrow incision ($n = 2$), and forehead incision ($n = 1$) according to the extent of FSO (Fig. 2). The forehead incision was preferred over the bicoronal incision in one patient as he was bald, and the authors of this work believed that an incision in a forehead crease would be more cosmetic than a bicoronal incision (Fig. 3). On the other hand, an exclusive endoscopic approach was done in 4 patients (Draf II in 3 patients and Draf III in 1 patient) (Fig. 4).

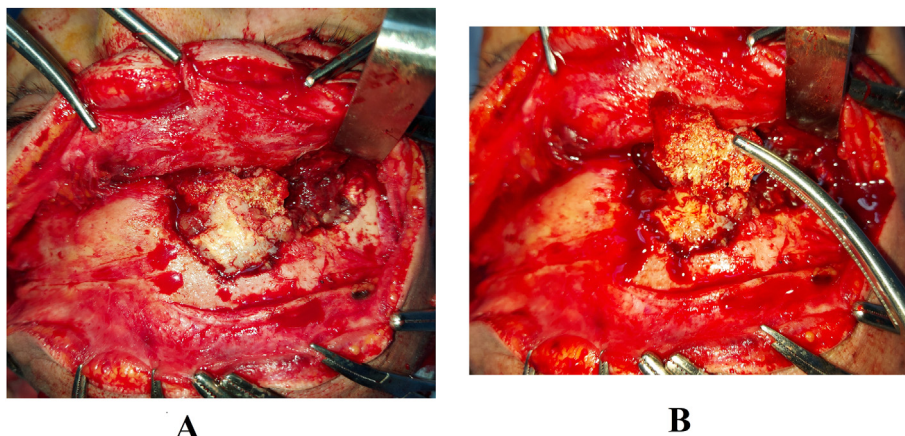


Fig. 2. Sequestrectomy through a coronal approach. A: Exposure of the sequestrum. B: Sequestrectomy.

After surgical debridement and sequestrectomy, specimens were sent for histopathological examination for confirmation of the IFS and determination of the causative organism from the morphology of the hyphae using hematoxylin and eosin (H&E), periodic acid-Schiff (PAS), and Gomori’s methenamine silver (GMS) staining. Moreover, specimens were sent for fungal culture for determination of the type of growth. The identified causative fungus of FSO was mucor species 17 patients, aspergillus in 1, and mixed infection with both mucor and aspergillus in 1.

As regards antifungal drugs, empirical treatment was started with IV amphotericin B (1 mg/kg/day) before waiting for the results of the culture. After obtaining the culture results, oral voriconazole (200 mg 12 hourly) was added for 2 patients when the culture revealed aspergillus growth. The duration of the antifungal treatment ranged from 4 to 8 weeks, until complete resolution of signs and symptoms, with monitoring of renal functions, liver functions, complete blood count, and blood sugar levels. All patients (n = 19)

completed the course of antifungal drugs with no reported major complications of treatment.

Postoperative healing was satisfactory in all patients (n = 19) (Fig. 5). Average postoperative clinical follow-up was 13.5 months (range 6–18). All patients returned to their normal daily activity within 4–6 weeks, without residual or recurrent frontal sinus infection, osteomyelitis or need for revision procedures.

3. Discussion

FSO may be caused by either bacterial or fungal infection. Bacterial FSO can be caused by Staphylococcus, Pseudomonas species, Streptococcus, and anaerobic organisms (Thompson et al., 2021; Nourkami-Tutdibi et al., 2020; Arnold et al., 2009; Hitti and Love, 2010), due to acute and chronic rhinosinusitis, previous surgery-induced obstruction of the sinus, and secondary to trauma (Thompson et al., 2021; Koltsidopoulos et al., 2020; Costa et al.,



Fig. 3. A: The forehead incision in the bald patient. B: Post-operative healing of the incision.

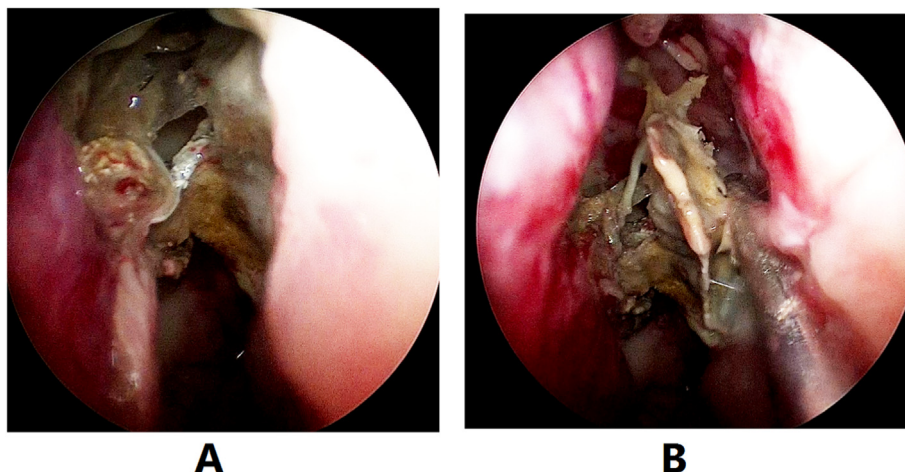


Fig. 4. Endoscopic treatment of FSO. A: Blackish gangrenous mucosa within the right frontal recess consistent with the diagnosis of IFS. B: Removal of the sequestrum from the right frontal sinus.

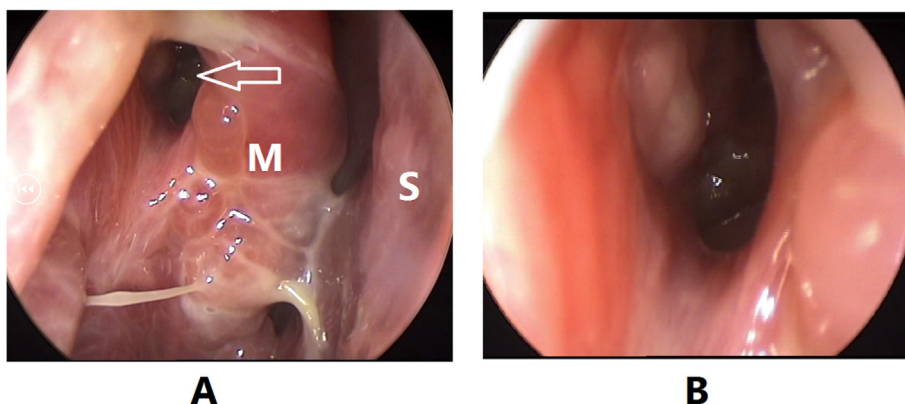


Fig. 5. Postoperative follow up endoscopy, 3 months after debridement, showing adequate healing. A: Patent right frontal sinus drainage (arrow). (M) is the middle turbinate. (S) is the nasal septum. B: A close view of the frontal sinus after introduction of an angled, 70° endoscope.

2020; Tatsumi et al., 2016). On the other hand, fungal FSO occurs in the setting of IFS due to bone ischemia and necrosis (Spellberg et al., 2005).

The main pathophysiological features of Mucorales infection are vascular invasion, with arterial thrombosis and subsequent ischemia and infarction of the soft and hard tissues. (Pogrel and Miller, 2003; Spellberg et al., 2005). On the other hand, aspergillus infection induces inflammatory cell recruitment to the infected site leading to tissue destruction (Chermetz et al., 2016). The germination and growth of fungal spores is facilitated by acidic environment, low oxygen, and high glucose level. Therefore, patients with uncontrolled diabetes are more susceptible to invasive fungal infections. Other contributing factors in diabetes include deranged granulocyte-phagocytic activity, altered polymorphonuclear leukocyte response, and microangiopathy and peripheral vascular disease, resulting in local tissue ischemia and increased vulnerability to infection (Kheirkhah et al., 2017; Tugsel et al., 2004).

In the current study, 16 out of 19 patients had insulin dependent diabetes mellitus. The identified fungal species was mucor in 17 patients, aspergillus in 1 patient and mixed mucor and aspergillus in 1 patient. Anehosur et al. (2019) reported mucormycosis in 44% of their patients, and aspergillosis in 2%, and other organisms in 54%. On the other hand, Srivastava et al. (2019) reported a case of maxillary fungal osteomyelitis, and the causative organism was concomitant fungal infection of mucormycosis and aspergillosis.

Fungal osteomyelitis of the maxillofacial region is rare (Verma et al., 2013). The commonest sites are the maxilla and the mandible (Peravali et al., 2012). Anehosur et al. (2019) in a series of 50 patients of maxillofacial fungal osteomyelitis over 12 years, identified that the most common site was the maxilla (56%), followed by the mandible (32%) and other sites (12%) such as extension into the eye or the frontal and ethmoidal region. The present case series includes 19 patients with the rare diagnosis of fungal FSO. The recent increased incidence of such pathology is concomitant with the increased incidence of IFS in post-COVID-19 patients.

Regarding the approaches for the management of FSO, traditional algorithms have suggested that open approaches are indicated in all cases to debride infected bone (Thompson et al., 2021). Similarly, the existing literature prefers open approaches for better access to the frontal sinus anterior table, especially laterally located or advanced disease. (Al-Qudah and Graham, 2012; Banks et al., 2018). In the current study, combined (open and endoscopic) approaches were utilized in 15 patients for complete debridement. On the other hand, in 4 patients, an exclusive endoscopic approach was performed as the sequestrum was small and easily accessible in the sinus. Consequently, sequestrectomy and adequate debridement were possible via the endoscopic approach. In the series of 16 patients of FSO by Thompson et al. (2021), pure open approaches were utilized in 6 patients, pure endoscopic in 7 patients and combined approaches in 3 patients. Chokkalingam et al. (2009) described a

completely endoscopic approach for fronto-cutaneous fistula closure secondary to FSO.

Although frontal sinus obliteration was performed by some authors for the management of FSO (Rimmer et al., 2019; Thompson et al., 2021), it was not performed by the authors of this work in this group of patients with IFS to avoid potential complications such as infection and mucocele formation. Accordingly, the sinus was preserved in all patients, and the patency of the frontal sinus outflow tract was maintained by performing Draf II or Draf III endoscopic approach. Furthermore, this wide drainage facilitates postoperative endoscopic follow up and sinus observation.

According to the Global guideline for the diagnosis and management of Mucormycosis (2019), (Cornely et al., 2019), an early complete surgical treatment for mucormycosis is strongly recommended whenever possible, in addition to systemic antifungal treatment. First-line treatment with liposomal amphotericin B is strongly supported.

In the current study, surgical debridement and sequestrectomy were the first line of treatment, along with empirical amphotericin B treatment. The treatment was started on just clinical suspicion of IFS and FSO, before obtaining the culture results as the delay in management is associated with increased morbidity and mortality. Voriconazole was added to treatment in 2 patients when aspergillus was diagnosed by fungal culture. Successful outcome was achieved in all patients of the study.

The limitation of this study is the small number of patients due to the rarity of the condition. Additionally, long term follow up is not available in all patients.

4. Conclusion

Within the limitations of this case series, it seems that there is no need to adopt a new therapy regimen for treatment of frontal sinus fungal osteomyelitis because the conventional and well-known treatment approach combining surgery and antifungal drugs seems to work well. However, early and adequate debridement and sequestrectomy is crucial. Furthermore, an open approach may be required according to the extent of osteomyelitis.

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Declaration of competing interest

The authors declare no conflicts of interest.

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