ORIGINAL ARTICLE

Invasive fungal rhinosinusitis, clinical manifestations, and prognostic values: as case series audit

Ali Rıza Yağmur[1*] , Ömer Faruk Çufalı[2] , Mustafa Çolak[2] , Şeyda Akbal Çufalı[2] , Ayşe Seçil Kayalı Dinç[2] , Agah Yeniçeri[2] , Nurcan Yurtsever Kum[2] and Kürşat Murat Özcan[2]

Abstract

Background Invasive fungal rhinosinusitis (IFRS) is a rare disorder with a high mortality rate. In this study, we reported four rare cases, two of them being the first reports in the literature, in addition, we reviewed retrospectively and discussed the effects of causative fungi, comorbid disorders, and intracranial involvement on mortality rate in 20 IFRS patients treated in the otolaryngology clinic between May 2019 and May 2021.

Results There were 10 (50%) males and 10 females with a median age of 51 years. Seven patients had rhinomaxillary, 11 had rhino-orbito-cerebral IFRS, and two had atypical presentations that could not be classified. The most frequent comorbid condition was diabetes mellitus (DM), and the most frequent causative fungi were Mucormycetes. There was no difference between DM and other comorbidity groups for orbital involvement ($p = 0.37$), intracranial involvement ($p = 0.17$), hard palate involvement ($p = 1$), cranial nerve palsies ($p = 0.17$), causative fungi ($p = 0.14$), or mortality ($p = 0.35$). Mucormycetes and other fungi were similar for orbital involvement ($p = 0.34$), intracranial involvement ($p = 0.16$), hard palate involvement ($p = 0.64$), and mortality rate ($p = 0.35$); however, cranial nerve palsies were significantly more frequent in Mucormycetes group ($p = 0.04$).

Conclusions Urgent diagnosis and multidisciplinary treatment are mandatory in IFRS. Due to its high mortality rate, IFRS should always be kept in mind in cases with atypical presentation, particularly if the patient is in the risk group. The current gold standard in IFRS management is urgent wide surgical debridement and concomitant administration of antifungals.

Keywords Invasive fungal rhinosinusitis, Complications, Treatment

Background

Invasive fungal rhinosinusitis (IFRS) is a rare and potentially fatal opportunistic fungal infection. Urgent diagnosis and management are mandatory due to high morbidity and mortality rates. Conditions such as uncontrolled diabetes mellitus (DM), hematological malignancies, solid organ transplantation, HIV infection, neutropenia, chemotherapy, and systemic use of corticosteroids are the main risk factors for IFRS [1]. IFRS is classified into three forms acute, chronic, and granulomatous forms [2].

The most common invasive fungal pathogens responsible for IFRS are *Zygomycetes/Mucormycetes (Rhizopus, Mucor, Absidia, Rhizomucor, Saxenaea, Apophysomyces, Cunninghamella)* and invasive *Aspergillus spp.* (*A. fumigatus, A. flavus, A. niger*) [3]. Although the patients with IFRS most frequently

*Correspondence:
Ali Rıza Yağmur
aryamur19@gmail.com
[1] Department of Otorhinolaryngology, Head and Neck Surgery, Ankara Lokman Hekim University, Ankara, Turkey
[2] Department of Otorhinolaryngology, Head and Neck Surgery, Ankara City Hospital, Ankara, Turkey

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present with the rhinocerebral form (rhinomaxillary, rhino-orbital, rhino-orbito-cerebral), cutaneous, central nervous system, pulmonary, gastrointestinal, renal, and disseminated forms may also be seen [4–6].

The symptoms are nonspecific such as nasal congestion, rhinorrhea, facial pain, headache, and fever in the early stages of IFRS [7], on the other hand, few or no symptoms may be seen in even advanced cases [1]. In addition to the aforementioned symptoms, facial swelling, loss of sensation in the face and nose, limitation of eye movements, and/or loss of vision should direct the physician to the pre-diagnosis of IFRS. The first step for early diagnosis is being alert for IFRS even in the presence of nonspecific symptoms in high-risk patients.

In this study, we reported four rare IFRS cases, reviewed 20 IFRS patients retrospectively, and discussed the effects of causative fungi, comorbid disorders, and intracranial involvement on the mortality rate. Case 1 is the first report of isolated nasopharyngeal IFRS in the literature. Case 2 has isolated sphenoid sinus IFRS, which is a very rare condition. Case 3 has bilateral orbital involvement, which is also very rare. Finally, Case 4 is the first case of IFRS in the literature caused by *Trichosporon ashaii*.

Methods
Data collection
This study is a retrospective case series. The electronic records of the patients with IFRS who were treated in our Otolaryngology Department between May 2019 and May 2021 were reviewed retrospectively to obtain data.

The demographic data, underlying comorbid disorders, and radiological images of the patients as well as the presence of any complications, the surgical debridement procedures, and the medical treatment administered were reviewed and recorded. The protocols for early diagnosis and treatment were also reviewed.

The patients with IFRS were divided into two groups in relation to the underlying disorder, the patients with DM and the ones with other conditions causing immunosuppression (hematological malignancies, medullary carcinoma of the thyroid, renal transplantation). These two groups were compared in terms of orbital and/or intracranial involvement, cranial nerve palsies, involvement of the hard palate, causative agents, and mortality rate.

In addition, the patients were divided into two groups in relation to the causative agent, as *Mucormycetes* group and the other invasive fungal pathogens group. These two groups were compared in terms of orbital and/or intracranial involvement, cranial nerve palsies, involvement of the hard palate, and mortality rate.

The diagnostic and management protocol for IFRS cases in our clinic
Otorhinolaryngological examination
The patients with suspected IFRS first undergo a detailed otorhinolaryngological examination including upper respiratory tract endoscopy (nasal endoscopy, nasopharyngoscopy, and laryngoscopy). Bedside endoscopic examination is performed in bedbound high-risk patients. On nasal endoscopy, pale mucosa and/or black necrotic areas may be seen; lack of bleeding is typical in the necrotic areas. This is the most important clinical diagnostic criterion for IFRS. In this step, a nasal biopsy is obtained for fungal culture.

Administration of systemic antifungals
Usually, the Infectious Diseases Department starts administering empirical systemic antifungals (amphotericin B) after clinical suspicion of IFRS by the Otorhinolaryngology Department. After obtaining the culture results, the Amphotericin B and liposomal amphotericin B are preferred for invasive *Mucormycetes*, and voriconazole is preferred for invasive *Aspergillus*.

Radiological imaging
All patients with suspicious or positive clinical findings undergo urgent paranasal sinus computed tomography (CT) and maxillofacial and cranial magnetic resonance imaging (MRI) with contrast to determine the extent of the infection within and out of the paranasal sinuses including subcutaneous tissue, pterygopalatine fossa, infratemporal fossa, orbita, and cranium (intracranial involvement). The radiological images are evaluated immediately by otorhinolaryngologists. The most striking radiological characteristic of IFRS is the involvement of an anatomic structure but a lack of contrast enhancement.

Surgery
Surgical debridement is performed on the same or the next day of the diagnosis, under general anesthesia. The endoscopic endonasal approach is preferred for surgical debridement. Intranasal structures including nasal septum and turbinates, ethmoid sinuses, medial and posterior walls of the maxillary sinus, lamina papyracea, and anterior wall of sphenoid sinus are usually removed. In fact, surgical debridement follows the areas involved in the radiological imaging, and intranasal structures as well as the contents and the walls of the paranasal sinuses are removed until they reach fresh, bleeding tissues. Surgical debridement may involve contents of the pterygopalatine fossa, periorbital fat, skin, hard palate, and even the orbit itself if the

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Ophthalmology Department decides that orbital exenteration is necessary.

Debrided material is sent for direct microbiological examination, fungal culture, and histopathological examination. During surgery, the Infectious Diseases or Clinical Microbiology Department reports the result of direct microscopic examination by phone, and a more extensive surgical debridement is performed if necessary. Even if the direct microscopic examination is inconclusive, or the result is inconsistent with the clinical findings of the patient, the necrotic structures are debrided. The debrided surgical area is washed with amphotericin solution, and absorbable packs impregnated with amphotericin are placed.

Follow-up and revision of surgical debridement

The nasal endoscopic examination is performed daily, and surgical debridement is repeated daily or every other day, depending on the nasal endoscopic findings. Revision debridements are performed in the operating room, under local anesthesia, with an endoscopic endonasal approach. First, the crusts inside the nose and sinuses are removed, and the walls of the debrided area are visualized and palpated. If present, necrotic tissues are debrided until they reach bleeding, healthy tissues. The aforementioned debridement procedure is performed at the bedside, in the intensive care unit if the patient's general condition is poor and cannot be taken into the operating room.

After two consecutive negative histopathological results for fungi, fungal infection is considered to be cleared, and surgical debridement is not performed anymore; however, the patients are still followed up with daily nasal endoscopy, particularly if the underlying condition (immunosuppression, diabetic ketoacidosis, etc.) is still active.

Reconstruction

Nasal and facial skin reconstructions are performed at least 3 months after discharge from the hospital. Those procedures are performed in collaboration with the Plastic and Reconstructive Surgery Department. Temporary hard palate obturators are prepared by Prosthetic Dentistry Department as soon as the patients' surgical debridements are over. Permanent obturators are prepared by the same department after discharge from the hospital. Ortibal prostheses are prepared by the Ophthalmology Department after the discharge of the patients.

Ethics approval was obtained from the institutional review board (No.1 clinical research ethics committee, E1-21-1931). Written informed consent was obtained from the patients to publish their photos in a scientific journal.

Statistical analysis

Basic statistical analyses were performed using the SPSS software (SPSS for Windows, version 21.0; SPSS Inc., Chicago, IL, USA). The chi-square test was used to compare the groups.

Results

The demographic characteristics, comorbidities, sites of involvement, pathogenic fungi, and outcomes of the patients are presented in Table 1.

Demographic characteristics and clinical presentation

Of 20 IFRS patients included in the study, 10 (50%) were male and 10 were female (Table 1). The median age of the patients was 51 years (IQR 18.5–64.8). The reason for hospitalization was usually non-specific, and the most common reason for admission to the hospital was poor general condition (35%), frequently secondary to the underlying condition. The reasons for otorhinolaryngology consultation were nasal congestion, headache, facial pain, hyperemia /swelling on the cheek, periorbital swelling, ptosis, limitation of eye movements, facial paralysis, and/or findings suggestive of IFRS on cranial CT performed for another reason. Paranasal sinus CT and MRI were performed in all patients to determine the extent of involvement.

Nasal cavity and paranasal sinuses were involved in 18 (90%) patients, 1 (5%) patient had isolated sphenoid sinus involvement, and 1 (5%) patient had isolated nasopharyngeal involvement. Hard palate invasion was seen in 9 (45%) patients (Fig. 1). Bilateral orbital involvement (Fig. 2) was detected in 1 of 11 (55%) patients with orbital involvement, and orbital exenteration was performed in two patients. Intracranial involvement was detected radiologically in 12 (60%) patients, and only one patient with intracranial involvement did not have orbital involvement. Cranial nerve palsies were detected in 8 (40%) patients (Fig. 3).

Comorbid conditions and patient outcomes in relation to comorbid conditions

All patients included in the study had at least one comorbid condition causing immunosuppression. DM was the most frequent comorbid condition and was present in 11 (55%) patients. Diabetic ketoacidosis was present in 5 of 11 patients with DM. One patient with DM had type 1 diabetes, and one patient with DM had IFRS after COVID-19.

Other comorbid conditions included hematological malignancies in 8 (40%), metastatic thyroid medullary

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Table 1 The demographic characteristics, comorbidities, sites of involvement, pathogenic fungi, and outcomes of the patients with IFRS

No	Age (years)/ gender	Comorbid condition	Orbital involvement	Intracranial involvement	Cranial nerve palsy	Hard palate involvement	Pathogenic fungus	Outcome
1	16/M	ALL	–	–	–	+	Trichosporon Ashaii	Died
2	11/M	ALL	–	–	–	–	Mucormycetes	Died
3	7/M	ALL	–	–	–	–	Aspergillus	Died
4	70/K	AML	+	+	–	–	Aspergillus	Died
5	18/M	AML	+ (Bilateral)	+	II, III	+	Mucormycetes	Died
6	54/M	DM	+	+	III, IV, V, VI	–	Mucormycetes	Died
7	71/M	DM	+	+	II, III, IV, VI, VII	+	Mucormycetes	Died
8	61/F	DM	–	–	–	–	Aspergillus	Survived
9	85/M	DM	+	+	–	–	Mucormycetes	Died
10	54/M	DM	+	+	II, VII	+	Mucormycetes	Died
11	57/M	DM	+	+	IV, VI, VII	–	Mucormycetes	Survived
12	50/F	DM	+	+	–	+	Mucormycetes	Died
13	49/F	DM	+	+	II, III, IV, V, VI, VII	+	Mucormycetes	Survived
14	20/M	DM (Type 1)	–	–	VII	–	Mukormikozis	Survived
15	51/F	DM, AML	+	+	–	–	Aspergillus	Died
16	66/F	DM, COVID-19	-	+	–	–	Mucormycetes	Survived
17	68/F	Metastatic thyroid medullary carcinoma	–	–	–	–	Mucormycetes	Survived
18	48/F	Pre B ALL	–	–	–	+	Aspergillus	Died
19	10/M	Pre B ALL	–	–	–	+	Mucormycetes	Survived
20	51/F	Renal transplantation	+	+	II, III, IV, V, VI	+	Mucormycetes	Died

ALL acute lymphoblastic leukemia, *AML* acute myeloid leukemia, *DM* diabetes mellitus, *IFRS* invasive fungal rhinosinusitis
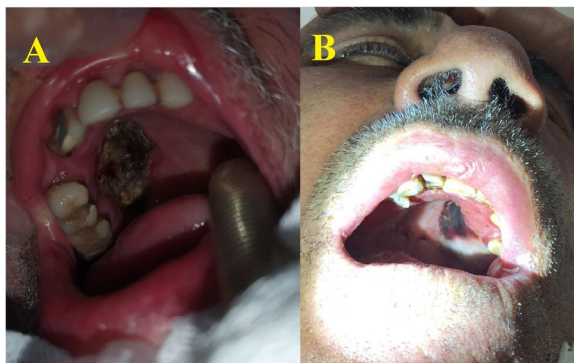

Fig. 1 Samples of hard palate involvement in patients (**A** and **B**) with invasive fungal rhinosinusitis

carcinoma in 1 (5%), and renal transplantation in 1 (5%) patient.

One patient had both DM and hematological malignancy.

In total, 13 (65%) patients died: eight had DM (61.5%) among whom 2 (15.4%) had diabetic ketoacidosis. In other words, the mortality rate was 72.7% (8/11) in the patients with DM. IFRS was mortal in 87.5% (7/8) of the patients with hematological malignancies.

DM and other comorbid conditions groups were compared for the extent of IFRS. No statistically significant difference was found between the two groups for orbital involvement ($p = 0.37$), intracranial involvement ($p = 0.17$), or hard palate involvement ($p = 1$). There were no statistically significant differences between the two groups for cranial nerve palsies ($p = 0.17$), causative fungi ($p = 0.14$), or mortality rate ($p = 0.35$).

Patient outcomes in relation to the causative fungi

Mucormycetes were detected in 14 (70%) patients, *Aspergillus* in 5 (25%) patients, and *Trichosporon Ashaii* in 1 (5%) patient. *Mucormycetes* were the most frequent causative agents.

The mortality rate was 57.1% (8/14) for the patients infected with *Mucormycetes*, 80% (4 /5) for the ones infected with *Aspergillus*, and 100% (1/1) for the ones infected with *Trichosporon Ashaii* (Table 1).

One patient infected with invasive Aspergillus had a defect on the nasal skin, reconstructive surgery was planned after recovery; however, the patient's general condition got worse and died (Fig. 4).
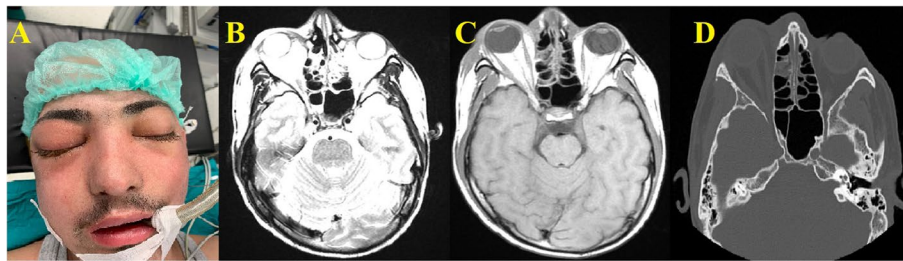
Fig. 2 A case of invasive fungal rhinosinusitis with bilateral orbital involvement. **A** Appearance of the patient. **B** T2-weighted axial MRI image. **C** T1-weighted axial MRI image. **D** Axial paranasal CT image

Fig. 3 The patient with cranial nerve II, III, IV, V, VI, and VII palsies. **A** Appearance of ophthalmoplegia. **B** Appearance of proptosis

A comparison of the patients infected with *Mucormycetes* and other fungi did not yield statistically significant differences for orbital involvement ($p = 0.34$), intracranial involvement ($p = 0.16$), or hard palate involvement ($p = 0.64$). On the other hand, the cranial nerve involvement rate was statistically significantly higher in patients infected with *Mucormycetes* ($p = 0.04$).

Mortality rates were similar in *Mucormycetes* and other fungi groups ($p = 0.35$).

Comparison of the patients with and without intracranial involvement for mortality

When patients with and without intracranial involvement were compared in terms of mortality, no statistically significant difference was found ($p = 0.35$).

Surgical procedures

Surgical debridement was performed with the endoscopic endonasal approach in all patients. Orbital exenteration was performed in two patients.

Case reports
Case 1

An 18-year-old male hospitalized for type 1 DM and diabetic ketoacidosis had hearing loss in his right ear as well as right peripheral facial paralysis. On his first physical examination, there was effusion in his right middle ear, House Brackmann grade 2 peripheral facial palsy on the right side of his face, and a mass resembling nasopharyngeal carcinoma on the right side of his nasopharynx on nasopharyngoscopy (Fig. 5). Paranasal CT and nasopharynx MRI were requested. Paranasal CT showed an asymmetrical mass in the right lateral pharyngeal recess of the nasopharynx, and minimal fluid in the right mastoid cells. MRI showed
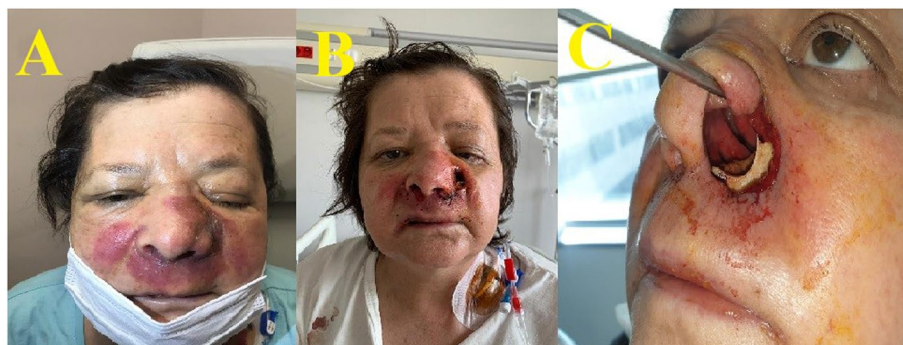

Fig. 4 Skin defect due to invasive Aspergillus infection. **A** Patient's appearance before treatment. **B** Appearance of skin necrosis during treatment. **C** Appearance of permanent defect on the nose skin
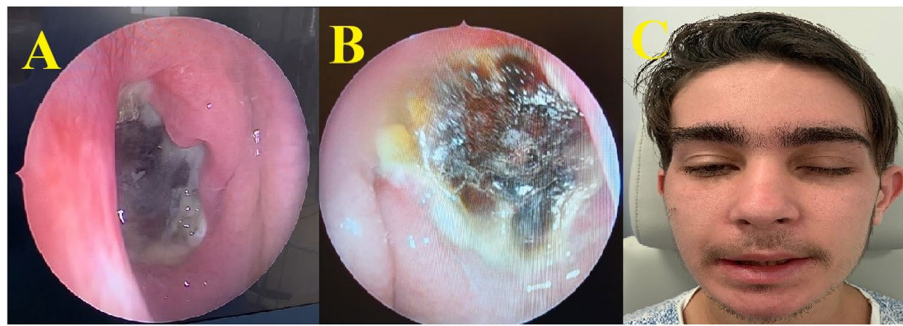
Fig. 5 Invasive Mucormycetes infection with isolated nasopharynx involvement. **A** and **B** Necrotic area in the nasopharynx. **C** Image of the patient's facial paralysis

a symmetrical mass in the nasopharynx compatible with adenoid hypertrophy, multiple retropharyngeal (the largest one 7 × 5 mm) and cervical (the largest one 22 × 13 mm) lymph nodes, as well as fluid in the right middle ear and mastoid. The next day, a necrotic area suggestive of IFRS was seen on the right side of the nasopharynx on nasopharyngoscopy, and a punch biopsy was obtained. The direct microscopic examination of the biopsy material revealed non-septate hyphae branching at right angles. The patient was diagnosed with IFRS, and the nasopharyngeal lesion was debrided by an endoscopic approach. Amphotericin B was administered simultaneously, and the patient was followed up closely. Daily nasopharyngoscopies did not reveal any nasal or nasopharyngeal necrotic lesions, therefore a second debridement was not performed. The patient was discharged and is still followed up (Table 1, patient no. 15).

Case 2

A 66-year-old COVID-19-positive female patient who was hospitalized for diabetic ketoacidosis underwent cranial CT due to a headache. She was consulted to the Otorhinolaryngology Department due to CT findings suggestive of IFRS, isolated to the sphenoid sinus. MRI did not show intracranial or orbital involvement. The patient was taken into the operating room under isolation precautions, and her sphenoid sinus was evacuated with an endoscopic endonasal approach. The histopathology report was "invasive mucormycosis", therefore the patient was administered amphotericin B, and followed up daily with the nasal endoscopic examination. After surgery and medical treatment, the general condition of the patient improved, and there was no suspicion of invasive fungal infection on either endoscopic examination or radiological images. The patient was discharged and is currently being followed up (Table 1, patient no. 16).

Case 3

Mucormycetes were isolated from the port-catheter culture of an 18-year-old male patient who underwent bone marrow transplantation for acute myeloid leukemia (AML) 75 days ago. The patient was consulted with the Otorhinolaryngology and Ophthalmology Departments due to hyperemia and edema around his right eye. On otorhinolaryngologic examination, both nasal cavities were filled with necrotic crusts, the right eye was proptotic, and there was edema, hyperemia, and warmth in the right eyelid and malar region (Fig. 2). The Ophthalmology Department determined total loss of vision in the right eye and impaired vision in the left eye. CT and MRI findings were suggestive of bilateral orbital cellulitis and IFRS. The patient was urgently administered antifungals and had wide endoscopic endonasal surgical debridement, and amphotericin B-impregnated sponges were placed into the debridement cavity. *Mucormycetes* were seen on direct microscopic examination of the surgical material. He was administered antifungal added nasal lavage; however, he deteriorated rapidly and died (Table 1, patient no. 5).

Case 4

A 16-year-old neutropenic male patient diagnosed with acute lymphoblastic leukemia (ALL) and underwent bone marrow transplantation was examined by the dentist for toothache, and diagnosed with acute periodontitis. The paranasal CT and MRI showed microabscesses of the dental roots. The patient was treated with multiple antibiotics, had a fever, and was consulted by the Otorhinolaryngology Department.

Otorhinolaryngologic examination revealed a necrotic region on the floor of the left nasal cavity and at the left side of the hard palate, between the canine and molar teeth. The necrotic region was surgically debrided. *Aspergillus* subspecies were seen on the direct microscopic examination of the surgical material; however, the culture

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result was *Trichosporon ashaii*. The patient was administered voriconazole and amphotericin B; however, he deteriorated rapidly and died (Table 1, patient no. 1).

Discussion

IFRS is a rare disorder and a high level of suspicion is needed for the diagnosis. It has an aggressive clinical course and a high mortality rate. Although previous studies reported the mortality rate of IFRS as high as 80% [8], this rate is reported as approximately 50% in recent studies [9]. IFRS should be kept in mind in the differential diagnosis, particularly in immunosuppressed patients, patients with uncontrolled DM, patients on chemotherapy or long-term corticosteroids, patients who underwent solid organ transplantation, and patients with hematological malignancies. In our study, we found the mortality rate of IFRS as 65%.

A study analyzed the results of 59 patients diagnosed with IFRS and reported that more than 60% of the patients had DM [10]. In another study reporting treatment outcomes in acute IFRS, DM ranked first among underlying disorders, followed by hematological malignancies [11]. On the other hand, Silveira et al. found DM (4.6%) rarer than hematological malignancies (58.2) and aplastic anemia (25.6%) [12]. In our study, DM was the most common (55%) comorbid condition, followed by hematological malignancies (40%).

A study on 43 patients with IFRS did not find any significant difference in mortality rates in relation to the primary disorder [12]. On the contrary, in their systematic review, Turner et al. found that the patients with DM had a higher survival rate compared to the patients with other comorbidities [9]. We divided our patients into two groups the patients with DM and the patients with other comorbid conditions, and we did not find any statistically significant difference between the two groups for extension of the disease (orbital involvement $p = 0.37$, intracranial involvement $p = 0.17$, cranial nerve palsies $p = 0.17$, hard palate involvement $p = 1$) or mortality rate ($p = 0.35$).

Various studies reported that Mucormycetes-related IFRS had a higher mortality rate compared to Aspergillus-related IFRS [13], while some others showed that mortality rates were similar for all fungus types [14]. In our study, we did not find any statistically significant difference in the mortality rate between the ones infected by *Mucormycetes* and by the other fungi ($p = 0.35$).

A study comparing the long-term orbital and neurological morbidities of *Mucormycetes* and *Aspergillus* infections reported that orbital and cranial nerve symptoms were more common in the *Mucormycetes* group, and there was no statistical difference in mortality between the two groups [15]. In our study, there was no

statistically significant difference in orbital involvement ($p = 0.34$) ($p = 0.16$), intracranial involvement, or hard palate involvement ($p = 0.64$) between the *Mucormycetes*-infected and the *Aspergillus*-infected groups; however, cranial nerve palsy rate was significantly higher in the *Mucormycetes* group ($p = 0.04$).

The mortality and morbidity due to IFRS is still quite high and the mortality rate of IFRS has been reported between 18% and 80% in different studies [8, 16]. Therefore, in case of clinical suspicion, the diagnosis should be made quickly, and if IFRS is diagnosed, it should be treated urgently and aggressively. In their series on 19 patients, Fernandez et al. reported that a treatment delay of more than 4 days was a negative prognostic factor [13]. In their treatment protocol, the patient was first evaluated with a sinus CT scan, then nasal endoscopy was performed, in the case of inconclusive endoscopic findings, an endoscopic nasal swab or biopsy was obtained, MRI was performed if the result was positive or if complications were suspected, medical treatment was administered in the presence of intradural involvement, and surgical + medical treatment were applied in the absence of orbital involvement and in case of extradural involvement [13]. In our clinic, we first evaluate suspected IFRS patients with a detailed head and neck examination and upper respiratory tract endoscopy. If the clinical and laboratory results of the patients are suspicious or positive for IFRS, we urgently order a paranasal sinus CT. In order not to miss the intracranial extension and its complications and to start treatment urgently, we also evaluate patients with MRI. Although Fernandez et al. reported that mortality was associated with the extension of IFRS and intracranial involvement was a poor prognostic factor [13], we did not find any statistically significant difference between the patients with and without intracranial involvement in terms of mortality. varying mortality rates in different studies may be related to the fact that the cause of death is not always clear and death may also be due to the underlying condition and not due to the fungal infection.

In some cases, the patient's clinical presentation may not always direct the physician to IFRS. In our study, a patient hospitalized with type 1 DM and diabetic ketoacidosis and consulted for right-sided hearing loss and peripheral facial paralysis was pre-diagnosed with nasopharyngeal carcinoma on his first endoscopic examination (Case 1, Fig. 5). Isolated nasopharyngeal involvement of IFRS was not reported in the literature before, and our case is the first patient reported with isolated nasopharyngeal IFRS (Case 1, Fig. 5). In addition, IFRS with isolated sphenoid sinus involvement, which is also rare and reported only in a few cases in the literature [17, 18], is also presented in one patient in our case series (Case

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2). Orbital involvement of IFRS is usually unilateral. Ashour et al. reported bilateral panophthalmitis in two cases with COVID-19 [19]. In our case series, one patient had bilateral orbital involvement (Case 3, Fig. 2).

El-Kholy et al. reported that the number of IFRS cases increased unexpectedly compared to previous years in the COVID-19 era [20]. Thirty-six patients with COVID-19 were included in their study, and it was reported that the main treatment option was antifungals, and the patients who did not have consecutive two negative PCRs were not treated with surgery [20]. Simultaneous IFRS and COVID-19 were diagnosed in one patient in our series (Case 2). This patient required surgical debridement, surgical debridement was performed by taking extra protective measures (using a powered air-purifying respirator), amphotericin B was administered simultaneously, and the patient survived after treatment. It is controversial whether surgical debridement should be performed on COVID-19-positive patients when their PCR is positive. PCR-positive patients should be evaluated individually, and surgery should be planned after taking both the benefit of the surgical procedure to the patient and the risk that the surgical team will take into consideration.

The most common causative agents are *Mucormycetes* spp. and invasive *Aspergillus* spp. in IFRS. In one of our patients, *Trichosporon Ashaii*, a member of the trichosporon species, was grown in the culture (Case 4). *Trichosporon Ashaii* is a yeast-like basidiomycetes. It is found widely in nature as well as in the normal flora of the human body and may become pathogenic in the case of immunosuppression [21]. Trichosporon Ashaii was not reported as the causative agent of IFRS before. Li et al. conducted an epidemiological analysis in 2020 to review *Trichosporon Ashaii* infections in the last 23 years, and revealed that this fungus caused urinary tract infection, fungemia, disseminated infection, lung infection, skin infection, chronic pneumonia, peritonitis, infective endocarditis, and brain abscess [22]. Hematological disorders were the most common underlying conditions in their patients, and DM was the second most common comorbid condition [22]. To our knowledge, our patient (Case 4) is the first IFRS patient in the literature infected with *Trichosporon Ashaii*, and he had ALL as the comorbid condition.

Conclusions

In conclusion, urgent diagnosis and management are mandatory in IFRS. A multidisciplinary approach is necessary since patients should be treated both for IFRS and the underlying condition. Due to its high mortality rate, IFRS should always be kept in mind in cases with atypical presentation, particularly if the patient is in the high risk group. The current gold standard in IFRS treatment is urgent wide surgical debridement and concomitant administration of antifungals.

Availability of data and materials
Not applicable

Declarations

Ethics approval and consent to participate
Ethics approval was obtained from the institutional review board prior to the initiation of the study. (Ankara City Hospital, No.1 clinical research ethics committee. Decree no: E1-21-1931). Written informed consent to participate in the study was provided by all participants and their parents or legal guardians in those who are under 16.

Consent for publication
Written informed consents for the publication have been obtained from the participants or their parents or from the next-of-kin or legally authorized representative in the case of the patients who have died whose age, gender, diagnosis, and images were given in the manuscript.

Competing interests
The authors declare that they have no competing interests.

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