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CASE REPORT

Confronting Acute Invasive Fungal Rhinosinusitis in a Malaysian Tertiary Health Care Centre

ERIC WANG YUAN LI[1,2]*, SITI HALIMAHTUN SAHAB[1], SITI SARAH RAZAK[1], NOORIZAN YAHYA@YAYAH[1], MOHAMAD KHIR ABDULLAH[1], HAFZAN BAHARIM[3], HARDIP SINGH GENDEH[2]

[1]Department of Otorhinolaryngology-Head & Neck Surgery, Hospital Pakar Sultanah Fatimah, 84000 Muar, Johor, Malaysia

[2]Department of Otorhinolaryngology-Head & Neck Surgery, Faculty of Medicine, Universiti Kebangsaan Malaysia, 56000 Cheras, Kuala Lumpur, Malaysia

[3]Department of Pathology, Microbiology Unit, Hospital Pakar Sultanah Fatimah, 84000 Muar, Johor, Malaysia

**Correspondence: ericwyl1505@gmail.com; Tel: +6012 3438353*

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ABSTRAK

Rinosinusitis kulat invasif akut (AIFRS) merupakan penyakit yang mencabar, yang lazimnya berlaku dalam kalangan pesakit imunokompromi. Keadaan ini dicirikan oleh perkembangannya yang sangat pantas. Walaupun terdapat kemajuan dalam rawatan perubatan dan pembedahan, kadar kelangsungan hidup bagi pesakit yang menghidapi AIFRS masih rendah. Selain itu, faktor-faktor yang mempengaruhi hasil rawatan pesakit bagi keadaan ini masih belum difahami sepenuhnya. Kami berkongsi pengalaman dalam menguruskan satu kes AIFRS. Diagnosis awal dan intervensi segera yang mungkin melibatkan pembuangan tisu mati melalui pembedahan yang agresif, pemberian ubat antikulat serta pengurusan faktor-faktor predisposisi adalah penting bagi membantu proses pemulihan. Pendekatan menyeluruh yang melibatkan pasukan otorinolaringologi, perubatan dan oftalmologi adalah penting bagi memastikan diagnosis dibuat dengan segera serta mengoptimumkan keadaan imunokompromi pesakit. Seterusnya, langkah ini dapat meningkatkan peluang kelangsungan hidup pesakit dalam jangka masa yang panjang.
Kata kunci: *Isavuconazole; rhizopus; rinosinusitis*

ABSTRACT

Acute invasive fungal rhinosinusitis (AIFRS) is a challenging disease which is commonly diagnosed in immunocompromised patients. They are characterised by its extremely rapid progression. Despite advancements in both medical and surgical treatments, the survival rates for patients with AIFRS are still limited. Additionally, the factors that influence patient outcomes in this condition are not well understood. We share our experience in managing a case of AIFRS. Early diagnosis and intervention, which may involve aggressive surgical debridement, antifungal medication and address underlying predisposing factors are critical for facilitating recovery. A comprehensive approach involving otorhinolaryngology, medical and ophthalmology teams are crucial for promptly diagnosing and optimising the underlying immunocompromised state. This approach can improve the patient's chances of survival in the long run.
Keywords: Isavuconazole; rhinosinusitis; rhizopus

INTRODUCTION

Fungal sinusitis is typically divided into non-invasive and invasive types (Bakhshaee et al. 2016). Non-invasive fungal rhinosinusitis includes allergic fungal rhinosinusitis and fungal ball and does not involve hyphae invading the mucosa (Bakhshaee et al. 2016; Goh et al. 2017). While examples of invasive fungal sinusitis are acute fulminant fungal sinusitis, chronic fungal rhinosinusitis and chronic granulomatous fungal rhinosinusitis are characterised by hyphal invasion of the mucosa (Bakhshaee et al. 2016; Goh et al. 2017). Acute invasive fungal rhinosinusitis (AIFRS) is potentially life-threatening and acknowledged as the most aggressive variant of fungal sinusitis (Bakhshaee et al. 2016; Vengerovich et al. 2020). The causes of this condition includes immunocompromised states (Bakhshaee et al. 2016; Vengerovich et al. 2020; Yağmur et al. 2023). Symptoms of this disease usually occur in less than a month and can be non-specific (Bakhshaee et al. 2016; Vengerovich et al. 2020; Yağmur et al. 2023). Diminished sensation in the face and nose, facial swelling, restricted eye movements, vision impairment should alert the physician to consider a preliminary diagnosis of AIFRS (Yağmur et al. 2023). Complications can occur if the disease is not detected early (Nyunt et al. 2021). Fungal agents causing AIFRS includes *Zygomycetes*/*Mucormycetes* (*Rhizopus*, *Mucor*, *Absidia*, *Rhizomucor*, *Saxenaea*, *Apophysomyces* and *Cunninghamella*) and *Aspergillus* spesies (*Aspergillus fumigatus*, *flavus* and *niger*) (Yağmur et al. 2023). Imaging modalities like computed tomography (CT) and magnetic resonance imaging (MRI) are often utilised for diagnosis and to assess potential orbital and intracranial extensions (Vengerovich et al. 2020). Since imaging findings can vary in specificity, histopathology showing angioinvasive fungi remains the gold standard for diagnosis (Vengerovich et al. 2020). Main treatment of AIFRS often involves a combination of aggressive surgical procedures, systemic antifungal therapy and management of underlying condition (Bakhshaee et al. 2016; Luo et al. 2023). Despite all these measures, mortality rates remain elevated, ranging from 18% to 80% (Bakhshaee et al. 2016). The objective of the case report was to describe a patient with AIFRS with nasal, orbital and intracranial involvement and to discuss the role of antifungal medications in the treatment of AIFRS.

CASE REPORT

A 58-years-old woman of Chinese ethnicity with diabetes mellitus, hypertension, dyslipidemia and left eye blindness due to advanced diabetic eye disease with total tractional retinal detachment presented with a week history of facial swelling. It started over the right cheek then progressively increased in size involving the periorbital area. She was treated with oral amoxicillin and clavulanic acid 625 mg bd for 1 week by primary care, but it did not resolve. She was afebrile. She had no nasal symptoms such as blocked nose, rhinorrhoea, sneezing or nasal itchiness. No history of toothache prior to onset of symptoms was recorded. She also had no increased intracranial symptoms, such as headache, vomiting or blurring of vision.

On examination, she had a full Glasgow Coma Scale (GCS), was normotensive with pulse rate of 93 beats per minute, afebrile and glucose monitoring of 15.6 mmol/L. There was a swelling over the right side of her face, superiorly from periorbital area inferiorly until the nasolabial region laterally from the right cheek until midline. The area was erythematous, tender and firm with loss of right nasolabial fold (Figure 1). Her cranial nerve examination was unremarkable. Anterior rhinoscopy showed presence of eschar over the right nasal cavity. Right nasoendoscopy showed presence of crusting with eschar over the entire inferior turbinate and septum, with no bleeding, mucupus or polyps (Figure 2). The patient had no pain sensation during nasoendoscopy. Right nasal swab was taken for culture and sensitivity and fungal stain.

Her total white blood cell was raised at 27 x 10^3/uL with neutrophil predominance. Contrast enhanced computed tomography (CECT) of paranasal sinuses (PNS) showed soft tissue density at right maxillary sinus. No bony erosions

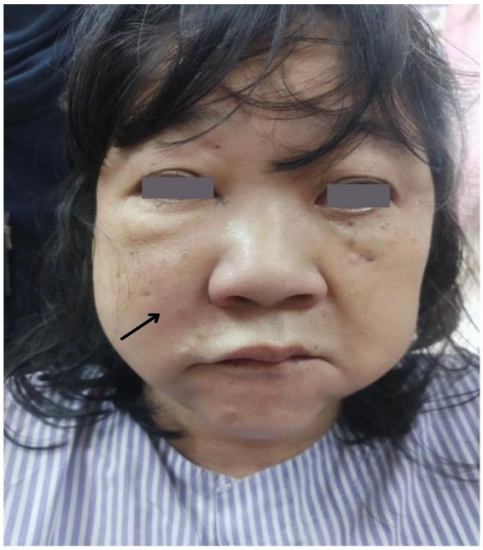

FIGURE 1: Right cheek swelling and redness (Black arrow) with loss of nasolabial fold and right periorbital swelling

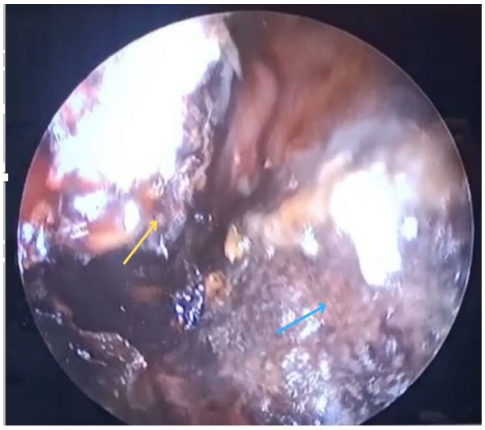

FIGURE 2: Right nasoendoscopic finding of eschar over the septum (blue arrow) and inferior turbinate (yellow arrow)

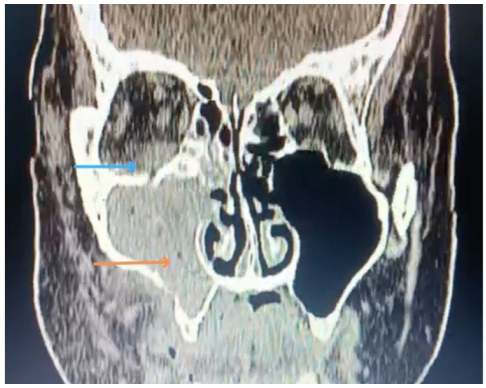

FIGURE 3: CECT PNS showing near complete opacification of the right maxillary sinus (Orange arrow). The right inferior rectus muscle was swollen (Blue arrow) and associated with increased adjacent intraconal fat streakiness. The rest of right extraocular muscles, right orbit and its content as well as left orbit content preserved

or calcification within were seen (Figure 3).

She was diagnosed with right AIFRS with preseptal cellulitis. Intravenous fluconazole 400 mg stat and once daily was started empirically. On ophthalmology assessment, her visual acuity was 6/36 with no relative afferent pupillary defect, normal anterior segment and full extraocular movement. She was treated as right eye preseptal cellulitis.

She underwent endoscopic sinus surgery with debridement of right inferior turbinate, right middle turbinate and septum until part of viable mucosa was seen. Eschar around maxillary antrum was debrided until bone was exposed. Part of involved septum cartilage was debrided and removed resulting in a large septal perforation. Histopathological examination showed numerous broad non-septated, non-pigmented fungal hyphae and acute angle branching septated hyphae within the necrotic material and the necrotic stroma. No blood vessel wall invasion. Her fungal culture showed densed growth of cotton candy-like which were white at first and then became brown- to blackish colonies as they matured. Microscopic examination revealed groups of long, unbranched sporangiophores and stolon which met together producing rootlike hyphae (rhizoids) consistent with the features of *Rhizopus* species (Figure 4).

Intravenous amphotericin B 60 mg OD and nasal douching with amphotericin B was started empirically for two weeks as antifungal sensitivity was not routinely done for *Rhizopus* in our center. Two weeks post-surgery, patient developed persistent temperature spike and we

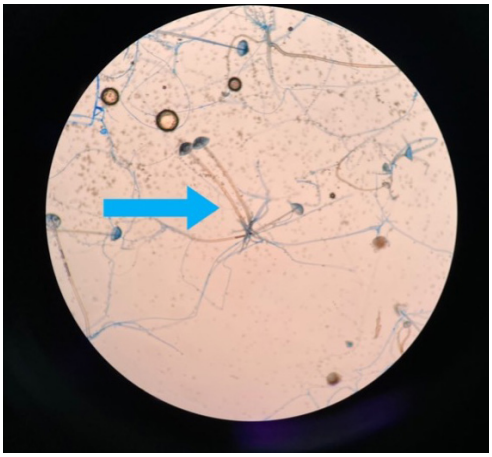

FIGURE 4: Figure showing a group of unbranched sporangiophores with rhizoid (blue arrow)

noticed presence of eschar over the right nasal cavity with extension into the left nasal mucosa over the septal region. CECT of PNS was repeated that showed the acute invasive fungal sinusitis had progressed into right ethmoid, frontal and sphenoid sinuses and cavernous sinus thrombosis (Figure 5).

Case was referred to the rhinologist and suggested for fungal deloading with posterior ethmoidectomy, sphenoidectomy and opening of the frontal recess. Surgery was performed as mentioned and repeated swab was taken. The repeated fungal swab culture and sensitivity was

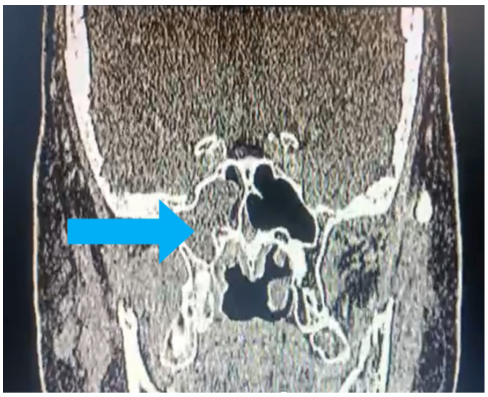

FIGURE 5: CECT PNS with blue arrow showing isodense soft tissue density over right sphenoid sinus

negative with culture of *Pseudomonas aeruginosa* and multidrug resistant *Enterobacteriaceae*. Intravenous and nasal douch of amphotericin B were continued for two months and changed to tablet posaconazole 300 mg once daily for for month. Repeated CECT PNS was performed after a month of oral antifungal and noticed progression of disease intracranially (Figure 6). Neurosurgeon was consulted and suggested for conservative treatment and not for surgical intervention. After discussion with Infectious Disease Specialist, we came into agreement for trial of isavuconazole in view of the fact that she was not responding to other antifungal agent. The patient then defaulted follow up as she was not keen to continue treatment. However, a follow-up call after a year revealed that the patient remained alive and was still uninterested in receiving treatment as she was afraid of the treatment side effects.

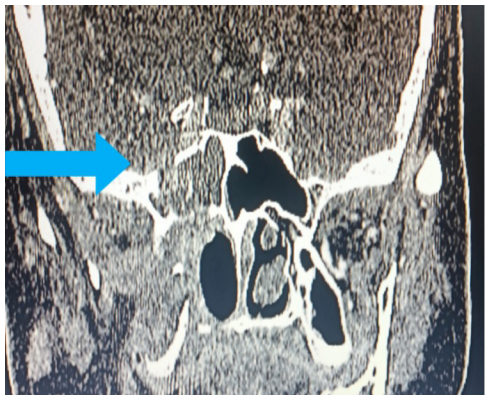

FIGURE 6: CECT PNS with blue arrow showing extension into right sphenoid sinus and new intracranial extension into right medial temporal lobe with no involvement of internal carotid artery

DISCUSSION

AIFRS is characterised by the infiltration of fungal hyphae into the sinus mucosa, submucosa, vasculature or bone, typically occurring within four weeks or less of the onset of sinusitis symptoms (Luo et al. 2023). It is an opportunistic infection that usually occurs in immunocompromised patients and is rarely seen in healthy people (Wu et al. 2018). Rhinocerebral forms such as rhino-

orbital, rhinomaxillary and rhino-orbito-cerebral are most commonly seen in patients with AIFRS but other forms including pulmonary, cutaneous, central nervous system, gastrointestinal, renal and disseminated presentations can also occur (Yağmur et al. 2023).

It is commonly seen in patients with uncontrolled diabetes mellitus (DM) and other immunocompromised state such as hematological malignancies, solid organ transplantation, human immunodeficiency virus infection, chemotherapy and systemic use of corticosteroids (Bakhshaee et al. 2016; Vengerovich et al. 2020; Yağmur et al. 2023). Like in our patient, she is a diabetic. Diabetic patients often experience impaired immune function, characterised by reduced chemotaxis and phagocytosis activity by neutrophils, monocytes and macrophages (Nyunt et al. 2021; Huang et al. 2021). Additionally, the combination of low oxygen tension, hyperglycemia can create an optimal environment for fungal growth and proliferation (Huang et al. 2021). Uncontrolled DM is a predisposing risk factor that can contribute to the progression of AIFRS (Huang et al. 2021).

Symptoms of AIFRS can be non-specific such as rapid onset of facial swelling, rhinorrhea, fever and nasal blockage. However, the most prevalent symptoms are typically headache and facial pain which may overlap with symptoms of viral or bacterial rhinosinusitis (Luo et al. 2023). Our patient came with a non-specific symptom of right facial swelling and denied having nasal symptoms. Physicians should take extra in patients who have alarming symptoms like reduced sensation to the face and nose, facial swelling, blurring of vision and restricted eye movements (Yağmur et al. 2023). Complications such as angioinvasion, extensive tissue necrosis, extension into the orbit, intracranial involvement and extension into the cavernous sinus can arise if there is a delay in diagnosis and treatment (Elmorsy et al. 2017; Nyunt et al. 2021).

Imaging like CT scan and MRI are required for diagnosing AIFRS. Most frequently observed CT scan findings are unilateral nasal cavity mucosal thickening and infiltration of the maxillary periantral fat planes by soft tissue which is similar to the finding of the CECT PNS in our patient (Luo et al. 2023; Vengerovich et al. 2020). Specific features such as orbital invasion, intracranial extension and bone dehiscence are indicative of advanced disease and may lead to poor prognosis which was seen in our patient as well (Luo et al. 2023; Vengerovich et al. 2020). The progression of disease on CT imaging did not correlate well with the patient's clinical presentation as the symptoms remained non-specific. MRI can be used in differentiating between mucus and edema and in evaluating the extent of intracranial and intraorbital involvement in AIFRS (Luo et al. 2023).

A confirmed diagnosis of AIFRS requires histopathological evaluation of biopsy tissue, complementing physical and radiological findings (Süslü et al. 2009). Employing hematoxylin and eosin (H&E) staining along with additional staining using periodic acid-schiff (PAS) and Gomori's methenamine silver (GMS) stain substantially enhances the diagnostic yield (Luo et al. 2023). The presence of hyphae within the submucosa, with or without angiocentric invasion along with tissue necrosis and minimal host inflammatory cell infiltration are the criteria used in histopathological diagnosis of AIFRS (Süslü et al. 2009). Mucosal abnormalities and suspicious lesions identified during nasal endoscopy should be biopsied concurrently (Süslü et al. 2009). In our centre, antifungal sensitivity testing is not routinely done. Fungal culture and sensitivity along with antifungal susceptibility testing can aid in identifying specific pathogens and guide the selection of appropriate antifungal agents (Luo et al. 2023). However, these detection methods are time consuming, so treatment initiation should be considered before receiving the final results (Luo et al. 2023). Therefore, in a low-resource setting, treatment should be started empirically which can carry risks of inappropriate drug selection, suboptimal dosing or resistance. Lack of sensitivity data also hampers tailoring treatment to individual patients, potentially leading to prolonged morbidity, higher recurrence rates and

increased healthcare costs.

The most frequently encountered causative agents in AIFRS are *Mucormycetes* spesies and invasive *Aspergillus* spesies (Yağmur et al. 2023). *Aspergillus* and *Mucor* species have the capability to invade vessel walls leading to thrombosis and ischemia (Süslü et al. 2009). Patients with poorly controlled diabetes are at a higher risk of *Mucor* infection and have a greater mortality rate compared to *Aspergillus* infections (Luo et al. 2023). As our patient was diabetic, *Mucor* infection (*Rhizopus*) was seen in her fungal culture. Whereas, *Aspergillus* infections are more common among patients with hematologic malignancies (Luo et al. 2023). *Rhizopus oryzae* is commonly reported as one of most prevalent organism responsible for 70-90% of cases of orbital mucormycosis (Huang et al. 2021).

Treatment requires a multidisciplinary approach by otorhinolaryngology, medical and ophthalmology teams (Süslü et al. 2009). Early correction of underlying diseases such as diabetes mellitus forms the basis for effective treatment of AIFRS (Luo et al. 2023). Similarly, our patient was referred to a multidisciplinary team to guide and properly treat her condition. After diagnosis, early debridement using endoscopic sinus surgery or open procedures remains crucial in reducing the incidence rate and mortality associated with AIFRS (Luo et al. 2023). Our patient also underwent two endoscopic sinus surgeries with debridement and fungal deloading. The primary goal is to decrease the fungal load through repeated debridement and enhance tissue penetration of antifungal medications (Luo et al. 2023). The surgical scope should encompass the removal of all necrotic and ischemic tissues to expose fresh wounds as extensively as possible (Luo et al. 2023). This includes resecting the necrotic sinonasal mucosa and addressing any suspicious turbinate or bone involvement (Luo et al. 2023). There remains a lack of consensus regarding the necessity and optimal timing of orbital exenteration in patients with ocular involvement (Luo et al. 2023). The decision to proceed with this procedure often necessitates ongoing communication between physicians and patients (Luo et al. 2023). There is currently no definitive evidence from existing studies indicating that orbital exenteration improves survival rates (Luo et al. 2023).

Apart from surgical debridement, the mainstay of medical management involves usage of antifungal medications (Vengerovich et al. 2020). All *Aspergillus* isolates showed sensitivity to voriconazole and posaconazole, whereas all *Rhizopus* isolates exhibited sensitivity to both amphotericin B and posaconazole (Elmorsy et al. 2017). Amphotericin B remains the primary treatment for the majority of AIFRS cases except for *Aspergillus* and other uncommon fungal species where voriconazole is preferred (Luo et al. 2023; Vengerovich et al. 2020). Due to potential side effects like hypokalemia and nephrotoxicity, the use of conventional amphotericin B is restricted (Luo et al. 2023). Liposomal amphotericin B which carries a lower risk of nephrotoxicity but comes at a higher cost, is often used as a substitute (Luo et al. 2023). Voriconazole used for invasive aspergillosis may require long term drug monitoring (Luo et al. 2023). Posaconazole is frequently used as a second-line agent instead of amphotericin because it is not primarily excreted by the kidneys thereby avoiding nephrotoxicity (Vengerovich et al. 2020). Isavuconazole, a newer broad-spectrum triazole is another alternative utilised in the treatment of *Mucor* and *Aspergillus* infections. It has lower nephrotoxicity compared to amphotericin and an improved safety profile in terms of side effects when compared to voriconazole (Vengerovich et al. 2020). Table 1 shows a summary of different antifungal agents that can be used in the management of AIFRS. For salvage therapies or severe cases like intracranial infections, the use of combination antifungal agents may be considered (Luo et al. 2023). Usage of topical amphotericin B showed better clearance of the disease due to the drug acting locally to reduce the fungal load (Nayak et al. 2022). In our patient, we started treating empirically with IV fluconazole then switching to IV amphotericin B. Tablet isavuconazole was started in view of patient not responding to the IV amphotericin B as evidenced by disease progression on CT scan. We also started the

TABLE 1: Summary of different antifungal agents used in the management of AIFRS

Antifungal agents	Indications	Susceptible microorganism	Side effects
Amphotericin B	Mainstay for the treatment of Mucormycosis	Rhizopus spp	Nephrotoxic, hypokalemia
Liposomal Amphotericin B	Can be used as a substitute for Amphotericin B	Rhizopus spp	Lower risk of nephrotoxicity
Voriconazole	Mainstay for the treatment of Aspergillosis and rare fungal infections	Aspergillus spp	Hepatotoxic, nephrotoxic, visual changes, hallucinations
Posaconazole	Second line treatment instead of Amphotericin B	Aspergillus spp, Rhizopus spp	Lower risk of nephrotoxicity
Isavuconazole	Alternative treatment for Aspergillosis and Mucormycosis	Aspergillus, Rhizopus spp	Lower risk of nephrotoxicity

patient on amphotericin B nasal douching similar to Nayak et al. (2022)

CONCLUSION

Despite years of research and efforts, AIFRS remains to be a disease with a high mortality rate and is a challenge due to its high invasive ability. A multidisciplinary approach involving both surgery and systemic antifungal therapy is essential as patients require treatment not only for AIFRS but also for the underlying condition contributing to their immunocompromised state.

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Conflict of interest: The authors declare no conflicts of interest.

Ethics statement: Not applicable.

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