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REVIEW

Egyptian Clinical Pathway for Post-coronavirus Disease 2019 Acute Invasive Fungal Rhinosinusitis

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Abstract

Acute invasive fungal rhinosinusitis (AIFRS) is a rare but fatal disease, particularly in immune-compromised patients, including those with hematological malignancies, poorly controlled diabetes mellitus (DM), and those who received immunosuppressive treatment following organ transplantation or chemotherapy for solid organ malignancies. Mortality rates remain high, around 50–80 %, though some recent studies have shown higher survival rates with early diagnosis and complete surgical resection. Surgical debridement, systemic antifungal therapy, and prompt correction of the underlying systemic disease are necessary for treatment of AIFRS. During the COVID-19 pandemic, an increased rate of AIFRS was reported in the course of; or following COVID-19 infections in our country and in other countries. This increased rate promoted us in RHINO-EGYPT society to make a task force of a group of qualified members to suggest a clinical pathway for management of these cases. The main aim was to specify the multidisciplinary team involved in the management with specification of the role of each department in the management. The suggested place for admission of the patient was determined according to the general condition of the patient and the status of COVID-19 infectivity. The criteria for diagnosis, management and discharge of patients were also specified. A final algorithm was produced and declared.

Keywords: Acute invasive fungal sinusitis, Coronavirus disease 2019, Mucormycosis, Treatment protocol

1. Background

Fungal sinusitis can be categorized into noninvasive and invasive types. The noninvasive form does not exhibit penetration of mucosa by hyphae while the invasive form is characterized by hyphae invasion to the mucosa and submucosal structures [1].

Acute invasive fungal rhinosinusitis (AIFRS) is defined by fungal hyphae infiltrating the sinus mucosa, submucosa, vasculature or bone, in the setting of 4 weeks or less of sinusitis symptoms. It’s considered one of the most serious diseases of nasal cavity and paranasal sinuses [2] due to vascular spread from nasal and sinus mucosa into the skull base, brain, and orbit [3].

Invasive fungal disease is a life-threatening infection affecting patients in immunocompromised state. Patients under intensive care due to influenza and respiratory viral infections including coronavirus disease 2019 (COVID-19) pneumonia are at an increased risk of developing invasive pulmonary fungal infections probably due to their reduced immunological competence [4].
Patients with COVID-19 pneumonia require intensive care, share risk factors and underlying diseases that make them vulnerable to invasive fungal infections [5]. During the COVID-19 pandemic, an increased rate of AIFRS was reported [6–8].

COVID-19 patients were found to have immune suppression attributed to a decrease in CD4+T and CD8+T cells [9]. In addition, COVID-19 affects immunity by depressing the neutrophilic response. It also causes overexpression of inflammatory cytokines (cytokine storm). These factors will ultimately lead to increased susceptibility to infections especially fungal infection [10].

It is important to consider that the use of corticosteroids which are prescribed for COVID-19 related complications may potentially reduce immune response especially if used in improper way. The already compromised immunological competence of the patients due to COVID-19 infection can be worsened by comorbidities and steroids [11]. In addition to steroids, the wide spread use of monoclonal antibodies and broad-spectrum antibiotics as part of the armamentarium against COVID-19 may lead to the development/exacerbation of preexisting fungal diseases [12].

A systematic review states that the overall survival rate of AIFRS patients is as low as 50 %. Early diagnosis and immediate treatment, including antifungal therapy and surgical debridement, are considered vital for better survival rates [13].

1.1. Diagnosis of acute invasive fungal rhinosinusitis

Early diagnosis entails first a high incidence of suspicion in immunocompromised patients and patients with COVID-19 infection. Early symptoms of AIFRS include fever lasting more than 48 h in patients with severe neutropenia [14]. Severe facial pain, facial numbness, headache, or anosmia might be the early presenting symptoms in addition to malaise [6]. Early endoscopic findings also include pale insensitive nasal mucosa, ulcers and black eschars in the nasal cavity in addition to palatal ulceration. Later on, atypical signs and symptoms similar to complicated sinusitis, such as nasal blockade, edema, proptosis, ptosis, chemosis, and even; ophthalmoplegia and rapid deterioration of vision. In addition, headache, fever and various neurological signs and symptoms might be present in cases with intracranial extension [15] (Fig. 1).

Computed tomography (CT) scans and MRI are needed to evaluate bone and soft tissue involvements (i.e. orbit/brain), respectively [16]. Radiological findings in early stages are usually nonspecific. Some imaging tests are completely normal despite the endoscopic findings suggestive of AIFRS [14]. Unilateral disease and bone thickening on CT scans are highly suggestive of the disease. Emphysematous or ulcerative mucosal changes in the nasal cavity are early imaging features of COVID-19 associated mucormycosis [16]. Periantral fat obliteration and presence of soft tissue within the pterygopalatine fossa might be present and are considered important imaging signs to indicate extrinsic invasion. Disease within pterygopalatine fossa may lead to multidirectional spread and is an important check site. These findings might happen even in absence of bony erosions owing to the neurovascular spread of disease. Intraorbital and intracranial extensions are fairly common late radiological signs and must be sought for [16].

MRI is used for accurate diagnosis and classification of AIFRS into localized sinonasal disease, then extension into maxillofacial soft tissue and bone and the more advanced intraocular and intracranial spread. MRI determines the extent of the disease and the required debridement. Involvement of the bone and MR-based staging were significant predictors of patients mortality [17].

The black turbinate sign (LOCE sign, lack of contrast enhancement, in T1 with contrast), balloononed sinus mucosa thickening; variable intensity within the sinuses on T1-weighted and T2-weighted images (predominant hypointense on T2); obliteration of the nasopharyngeal planes, preantral fat infiltration, loss of contrast enhancement of the sinonasal mucosa and extraocular muscles (T1 with contrast), inflammatory changes in peri-antral area, orbital content (predominant hyperintense on T2 fat suppression), and cerebral leptomeningeal enhancement were all previously documented MR findings of AIFRS [18] (Fig. 2).

Presence of fungal hyphae invading sinus mucosa is the definite diagnosis of mucormycosis tissue. Despite histopathological diagnosis is mandatory for establishment of diagnosis, it is challenging due to misidentification of Mucorales and Aspergillus species in specimen [19]. New techniques are used, such as monoclonal antibodies or PCR techniques on either fresh or formalin-fixed paraffin-embedded tissue to improve diagnostic specificity [20].

Serology has a role in diagnosis of AIFRS especially detection of Galactomannan (specific for Aspergillosis) and β-D glucan (panfungal antigen except for the mucormycosis and cryptococcosis) in serum and/or bronchoalveolar lavage. These tests cannot distinguish between surface colonization and true pathogen invasion, so these tests have a high negative predictive value, that is false-positive result can be observed [21].
When diagnosis is established, treatment should be immediately started, including antifungal therapy and surgical debridement. This regimen is considered vital and extremely important for better survival rates [21]. Early treatment is recommended to the degree that some support to start the antifungal therapy before the pathological diagnosis is settled [16].

1.2. Medical management

Prophylactic antifungal protocol was recommended in all vulnerable immune-compromised patients to prevent this fatal condition. The recommended medication is posaconazole [22].
1.2.1. Therapeutic antifungal protocol

Monotherapy; liposomal amphotericin B (Ambisome) 5–10 mg/kg per day is strongly recommended in all organ involvement. If substantial renal toxicity develops, the dose can be reduced. Azoles, for example, isavuconazole and posaconazole are recommended as first-line treatment of mucormycosis, voriconazole as first-line in treatment of invasive Aspergillosis [23].

(1) Combined therapy; there is no consensus in literature about antifungal combination therapy. It can be rationally given due to lack of enhanced toxicity with possible but unproven benefits. It is recommended in intracranial involvement, disseminated mucormycosis and in patients with hematological malignancy [24].

(2) Antifungal salvage treatment; due to treatment failure, refractory mucormycosis or toxicity of first-line regimens. Amphotericin B formulation failure could be replaced by isavuconazole or posaconazole either delayed release tablets or infusions. On other hand, Azoles failure could be substituted by any amphotericin B lipid formulations [25].

1.2.2. Treatment duration for acute invasive fungal rhinosinusitis

The treatment duration necessary to treat AIFRS is unknown. It relied on controlling of immune status and resolution of fungal infection. Antifungal therapy should continue till permanent reversal of immunosuppression and complete healing of nasal mucosa detected by endoscopic finding or by imaging. The treatment strategy is personalized, range from 1 month to 3 years, average duration is 3 months [25].

1.3. Surgical management

1.3.1. Disease confirmation – tissue biopsy

Middle turbinate is condemned to be the first affected nasal structure, so middle turbinate biopsy is considered as safe effective method in diagnosis of AIFRS with high specificity/sensitivity value (100–75 %, respectively) [26].

(1) Surgical debridement of all necrotic tissue till reaching a vascular plane is mandatory in surgical management of rhino-orbital-cerebral mucormycosis. Sinonasal affection is managed by surgical debridement of all diseased and necrotic tissue. The pterygopalatine fossa and infratemporal fossa are considered as fungal hyphae reservoir where the invasion of sphenopalatine vasculature by fungal hyphae leading to thrombophlebitis and subsequent nasal and PNS mucosal tissue ischemia and necrosis. Extended endoscopic approaches may be required to get access to surgical hidden areas pterygopalatine fossa and infratemporal fossa, especially modified endoscopic Denker approach (Fig. 3).

(2) Orbital necrosis (orbital fat, ocular muscles) is usually associated with ethmoidal vessel affection leading to nonfunctioning eye – proptosis. Endoscopic orbital decompression only versus exenteration is considered to eliminate all fungal loads (Fig. 4).

(3) Palatal necrosis usually results from affection of greater palatine vessels. Surgical excision (inferior maxillectomy) is required with dental rehabilitation by obturator in early postoperative
period to prevent soft tissue contracture and enhance feeding.

(4) Cutaneous mucormycosis with involvement of facial skin is managed by debridement till reaching viable skin margin. Skin care in post-operative period is done by daily dressing, frequent debridement till stabilization of patient condition then plastic reconstruction take place in form of loco-regional flaps.

(5) Intracranial affection is managed by combination antifungal therapy with considering anticoagulant therapy. Neurosurgical intervention could be required in fungal abscess formation (Fig. 5).

1.4. Precoronavirus disease 2019 versus coronavirus disease 2019 mucormycosis

COVID-19 associated mucormycosis CAM had high incidence with relatively less mortality rate than pre-COVID-19 mucormycosis. Main offending risk factors in addition to viral infection were diabetes mellitus and steroid therapy; mortality rate was 35.9 % in CAM. On other hand, pre-COVID-19 mucormycosis was related mainly to hematological disease with 64.6 % mortality rate [27].

1.5. Prognosis and outcome

AIFRS is a rare but fatal disease up to 50–80 %.

Prognosis depends up on fungal virulence, host immunity, and initiation of management plan either antifungal therapy or surgical debridement.

(1) Mucorales (mucor, rhizopus, rhizomucor, etc.) species are more virulent with worse prognosis than aspergillosis.

(2) Noncorrectable immune-compromised state especially hematological oncology, pancytopenia carries bad nadir in comparison to controlled immunity situation.

(3) Early management is considered the only weapon to deal with this fatal condition, initiate antifungal therapy once AIFRS is clinically suspected without waiting for delayed histopathological results.

Certain bad prognostic features in COVID-19 associated mucormycosis (CAM).

(1) Interval between AIFRS development and COVID-19 pneumonia (concomitant COVID-19 infection and AIFRS or interval below 2 weeks had higher mortality rate) [26,28].

(2) Mucor palatal osteomyelitis/facial bone osteomyelitis had a rapid progressive course.

(3) Initial CRP over 200–250.

(4) Oxygen saturation below 90 % in room air.

(5) Poor control of DM, DKA, and high level of HbA1C at time of admission are considered poor prognostic factors which affects survival. A level below 9.35 % was associated with better survival [29].

1.6. Egyptian clinical pathway

Ten experts from different institutions from all over Egypt, who were involved comprehensively in the management of AIFRS cases during COVID-19
pandemic, were recruited. Every one of them was involved in the management of at least 20 cases of AIFRS cases during the pandemic and has at least one publication in the management of AIFRS. This pathway was conducted through review of publicly available literature and did not involve patients or specific clinical data. The pathway was developed in the period from April 2021 to August 2021 through online meetings.

The general coordinator of the pathway specified the most important points of concern in management of AIFRS and distributed them among the experts. The points of weakness in the management in the Egyptian practice during the pandemic were stressed on. Every expert was asked to review the literature for best evidence, in a narrative manner, to answer the questions raised. Along four online sessions, the results were formatted in the form of an algorithm for management and voting were arranged to agree or disagree on the algorithm and path of management. The final version was reviewed by all the experts and approved.

No international experts were involved as the main issue was to present the Egyptian experience as a developing country for future validation of the clinical pathway and algorithm in other countries. In addition, the high prevalence of AIFRS after COVID-19 was only noticed in only very few countries other than Egypt.

Although this pathway was developed during the COVID-19 era, it can be applied to nonpost-COVID-19 AIFRS patients. The main points of difference are the state of infectivity, the place of admission and the timing of surgical intervention which can be modulated or changed and can be suitable if future similar pandemics happened.

The suggested pathway for managing COVID-19 associated invasive fungal rhinosinusitis specifies the multidisciplinary team involved in the management, the place of admission of the patients according to the state of COVID-19 infection and the full protocol of management (Figs. 6 and 7).

Any immune-compromised patient or patient with recent history of COVID-19 infection with persistent nasal symptoms is considered AIFRS till prove otherwise with ORL referral for diagnostic protocol.

The stepladder protocol consists of clinical endoscopic suspicion, radiological CT and MRI probability and finally histopathological certainty. Once clinical suspicion occurs, start empirical antifungal therapy. In addition to the known radiological signs of AIFRS. The black middle turbinate sign in MRI T1 with contrast has high positive predictive value up to 92 %. MT biopsy has high specificity/sensitivity value (100-75 %, respectively) [26,28].

Once patient is fit for surgery, necrotic tissue debridement should be initiated as soon as possible

Fig. 6. Multidisciplinary team involved and where to admit patients with AIFRS. Each clinical subspeciality was offered a number. AIFRS, acute invasive fungal rhinosinusitis.
(sino-nasal debridement, skin debridement, palatal excision and orbital exenteration).

Postoperative empirical antifungal therapy (liposomal amphotericin B – Ambesome) is recommended to continue till appearance of results of fungal culture and sensitivity. During follow up period, assessment of patient general condition, endoscopic findings, inflammatory marker response (ESR and CRP) is done every other day. Then weekly follow up regimen in first postoperative month and monthly follow up till complete resolution of infection. Shift to alternative or combined therapy or re-admission or re-intervention will be judged according to the clinical and radiological response of the patient (Fig. 7).

1.7. Conclusion

An increased incidence of AIFRS was seen in some countries during the COVID-19 pandemic and can be a concern in similar future pandemics. Management should include a multidisciplinary team where the responsibilities are specified. In addition to knowledge and avoidance of the predisposing factors, high clinical suspicion, early diagnosis and management are crucial for optimizing the outcome of this potentially fatal condition.

Conflicts of interest

There are no conflicts of interest.

References