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Early diagnosis of mucormycosis in COVID-19 patients by computerized tomography scan and biopsy in intensive care unit patients with COVID-19

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Abstract---Introduction: coronavirus disease-2019 (Covid-19) cases were increasing a while ago with rising in morbidity and mortality rates. severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infected patients have many variant presentations from asymptomatic up to severe acute respiratory syndrome. Objective: The aim of this work was a trial of early diagnosis of mucormycosis in covid-19 patients that need ICU admission using CT scan and histopathology. Materials and methods: This prospective study was carried out on 64 patients with covid-19 who received steroid therapy. All patients were subjected to computerized tomography scan on the nose and paranasal sinuses, request for ophthalmology and neurology for further assessment and extension of complications, surgical debridement of necrosed tissue (when patients fit for surgery), histopathology, confirming the diagnosis of mucormycosis. Results: Duration between covid infection and mucormycosis infection was ≤ 15 days in 17 patients (26.6%), more than 2 weeks up-to 4weeks (one month) in 45 patients (70.3%), and two months in 2 (3.1%).

Conclusions: The incidence of mucormycosis is likely to rise, both as a co-infection and as a sequela of COVID-19. Early diagnosis and management with appropriate and aggressive antifungals and surgical debridement can improve survival.

Keywords---biopsy, CT scan, COVID-19 patients, ICU, mucormycosis.

Introduction

Coronavirus disease-2019 (Covid-19) cases were increasing a while ago with rising in morbidity and mortality rates. severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infected patients have many variant presentations from asymptomatic up to severe acute respiratory syndrome (Parasher, 2021). There are many modalities in the treatment of COVID-19 disease such as antiviral drugs and immunomodulatory agents as steroids and other drugs still under research (Bartoli, Gabrielli, Alicandro, Nascimbeni, & Andreone, 2021). Glucocorticoid is an important immunomodulator in severe cases of COVID-19, but glucocorticoid dosage and duration should be fully modified for fear of side effects (Yang & Yu, 2021).

Plenty of research recording COVID-19 complications such as pneumonia, respiratory failure, acute kidney failure, sepsis, myocarditis, disseminated intravascular coagulation, pneumothorax and others (Murk et al., 2021). Patients with COVID-19 disease (severe form) may develop fungal infections such as invasive pulmonary aspergillosis, invasive mycosis and invasive candidiasis. Mucormycosis which cause invasive fungal disease is increasing nowadays. Predisposing factors for such cases are diabetes mellitus (40%) corticosteroid use (33%) cancer chemotherapy (18%). Many symptoms have implemented such as rhino-orbital-cerebral mucormycosis (34%), cutaneous mucormycosis (22%), pulmonary mucormycosis (20%) (Jeong et al., 2019).

It is reported that diabetic COVID-19 patient co-infected with mucormycosis. Also, comprehensive use of corticosteroids and broad-spectrum antibiotics may be accused in mucormycosis formation (Mehta & Pandey, 2020). Rhino-orbital-cerebral mucormycosis presented with diminution of vision, ophthalmoplegia and proptosis especially with uncontrolled diabetic patients. The most common sinus convoluted in mucormycosis is the ethmoid sinus (Gupta, Goyal, & Kaore, 2020). Mucormycosis is a disease with high morbidity and mortality, also it gravitates to progress rapidly. So, we must start medical and surgical treatment early to save patients (Cornely et al., 2019).

We can investigate mucormycosis by computerized tomography (CT) scan and histopathology. CT scan of mucormycosis patients shows thickening mucosa, incomplete opacity of paranasal sinuses (PNS), orbital and intracranial complications (Serris, Danion, & Lanternier, 2019). Histopathology sometimes cannot discriminate between *Aspergillus* hyphae and *Mucorales* hyphae, but it is still the cornerstone for the diagnosis of mucormycosis (Skiada et al., 2018). Intensive care unit (ICU) admission for mucormycosis patients after surgical debridement is important due to comorbidities and high mortality rate

(Karaaslan, 2019). In this study, we will study the early diagnosis of mucormycosis in covid-19 patients in Egypt by CT and histopathology. The aim of this work was a trial of early diagnosis of mucormycosis in covid-19 patients that need ICU admission using CT scan and histopathology.

Materials and Methods

This prospective study was carried out on 64 patients aged above 40 years old with covid-19. The study took place at Otorhinolaryngology department. An informed written consent was obtained from the patients. The study was done after approval from the Ethical Committee of Helwan University.

Inclusion criteria

Covid-19 patients who received steroid therapy, diabetic and having sinonasal symptoms.

Exclusion criteria

Patients below 40 years old, with hematological malignancy, receiving cancer chemotherapy or with organ transplantation. All patients were subjected to history taking, clinical examination (general and local), computerized tomography (CT) scan on the nose and paranasal sinuses, request for ophthalmology and neurology for further assessment and extension of complications, surgical debridement of necrosed tissue (when patients fit for surgery), histopathology, confirming the diagnosis of mucormycosis, the COVID-19 infection was categorized according to World Health Organization (WHO) guideline: mild, moderate and severe (Organization, 2020), for attributing the clinical form of mucormycosis, the location and extension of the disease, CT scan of the orbit, paranasal sinuses and lung were used.

Computed tomography (CT) of the sinuses uses special x-ray equipment to evaluate the paranasal sinus cavities – hollow, air-filled spaces within the bones of the face surrounding the nasal cavity. CT scanning is painless, noninvasive and accurate. It is also the most reliable imaging technique for determining if the sinuses are obstructed and the best imaging modality for sinusitis. Histopathology is a very important diagnostic tool since it distinguishes the presence of the fungus as a pathogen in the specimen from a culture contaminant and is indispensable to define whether there is blood vessel invasion. It can furthermore reveal coinfections with other molds. Mucorales genera produce typically non-pigmented, wide (5–20 μm), thin-walled, ribbon-like hyphae with no or few septations (pauciseptate) and right-angle branching, in contrast to those of the *Aspergillus* species or other hyaline molds, which are typically 3–5 μm wide, septate and form acute-angle branching. Routine hematoxylin and eosin (H&E) stains may show only the cell wall with no structures inside, or occasionally, very degenerate hyphae. Stains that can help highlight the fungal wall include Grocott methenamine-silver (GMS) and periodic acid-Schiff PAS stains, although PAS gives a better visualization of the surrounding tissue compared to GMS.

Sample size justification

The sample size calculation was performed using G. power 3.1.9.2 (Universitat Kiel, Germany). The sample size was calculated based on the following 0.05 α error, 80% power and the expected incidence of mucormycosis in Covid-19 patients ranged from 40.6% to 78.9% according to a previous study (Singh, Singh, Joshi, & Misra, 2021)). Fourteen cases were added to overcome dropout. Therefore, 64 patients were recruited. 64 covid-19 patients who received steroids or have diabetes mellitus were selected from the outpatient clinic of Helwan University Hospitals, with external referral from other centers.

Statistical analysis

Statistical analysis was done by SPSS v26 (IBM Inc., Chicago, IL, USA). Quantitative variables were presented as mean and standard deviation (SD) and compared between the two groups utilizing unpaired Student's t- test. Qualitative variables were presented as frequency and percentage (%) and were analysed utilizing the Chi-square test or Fisher's exact test when appropriate. A two tailed P value < 0.05 was considered statistically significant.

Results

Table I shows demographic data and clinical signs of the studied patients. Table II shows computerized tomography scan and biopsy of the studied patients. Table III shows Symptoms Eye, and clinical and duration between covid and mucor of the studied patients.

Discussions

Acute COVID-19 disease is commonly complicated by prolonged symptoms that can often last for months (Salamanna, Veronesi, Martini, Landini, & Fini, 2021). These symptoms can include fatigue, dyspnea, cognitive and mental impairments, chest pains, joint pains, palpitations, myalgias, alterations or loss of taste or smell, cough, headache, and GI distress (Rank et al., 2021).

Hussain et al., (Hussain et al., 2021) performed meta-analysis comprised six studies with a pooled sample size of 52,916 COVID-19 patients with a mean age of 62.12 ± 9.69 years. The pooled prevalence of CAM Covid-19 (seven cases per 1000 patients) was 50 times higher than the highest recorded background of mucormycosis (0.14 cases per 1000 patients). As CAM is a rare disease and of low prevalence there are many published case reports worldwide. Diagnosis of CAM is a major challenge in patients with COVID-19 due to avoidance of respiratory samples or bronchoscopy.

In our study age of the studied patients ranged from 40-73 years with a mean of 54.86 ± 9.80 years. There were 23 (35.9%) males and 41 (64.1%) females in the studied patients. All cases were uncontrolled DM, post covid, and ICU admission, 41 (64.1%) were hypertensive. The deviation from our results may be attributed to that they selected their cases in the early appearance of mucormycosis post covid-19, there was limited number of cases at this time yet ours as we performed our

study after more than one year and mucormycosis became more common complication in high number of cases worldwide.

Additionally, Sen et al., (SenHonavar, et al., 2021) published another article in the same year titled as epidemiology, clinical profile, management, and outcome of COVID-19-associated rhino-orbital-cerebral mucormycosis in 2826 patients in India – collaborative OPAI-IJO study on mucormycosis in COVID-19 (COSMIC). Their study aimed to determine the patient demographics, risk factors including comorbidities, and medications used to treat COVID-19, presenting symptoms and signs, and the outcome of management. This was a retrospective, observational study of patients with COVID-19-associated ROCM (Rhino-orbital-cerebral mucormycosis) managed or co-managed by ophthalmologists in India from January 1, 2020, to May 26, 2021. They studied 2826 patients in different states at India. The mean age of their patients was 51.9 years. But in contrast to our findings, they reported that males were predominant (71%). DM was present in 78% among their patients.

In agreement with our findings, Arora et al., (Arora et al., 2022) carried out a case-control study during the outbreak in India comparing cases diagnosed with CAM associated mucormycosis) and those who had recovered from COVID-19 without developing mucormycosis (controls). Information on comorbidities, glycemic control, and practices related to COVID-19 prevention and treatment was recorded. They enrolled 352 patients (152 cases and 200 controls) diagnosed with COVID-19 and documented that the mean age of cases was 49.4 ± 11 . Diabetic cases were 140 (92.1%).

However, their patients were 40 (70.12%) male and 17 (29.82%) female patients. The difference in male to female ratio from our results may be explained by that it is related to the immunity status of the patient and comorbidity not to the gender (Azhar et al., 2022). In our study, 54 patients (84.38%) of the studied patients had no cardiac symptoms while 10 patients (15.6%) had cardiac symptoms. 57 patients (89.06%) had no hepatic or renal symptoms, while 5 patients (7.81%) had renal symptoms and 2 patients (3.13%) had hepatic symptoms.

In the same line with our findings, Solanki et al., (Solanki, Solanki, Madaliya, Jasoliya, & Upadhyay, 2022) observed that among comorbid patients, history of coronary artery bypass grafting was noted in two patients and angioplasty also in three patients. Furthermore, Arora et al., (Arora et al., 2022) documented that chronic kidney disease was in 12 (3.4%); 7 (2%) of them had maintenance hemodialysis and 3 (0.6%) with post-renal transplant. In our study, regarding CT scan, unilateral opacity was more common than bilateral opacity. As shown in figure 3. As there are a limited number of published studies concerning CAM diagnosis, we included some case reports in this area.

Sethi et al., (Sethi et al., 2021) reported a case report 55-year-old male was admitted in the COVID-19 ICU for a period of 2 weeks and treated according to the existing protocols, including steroids and ventilator therapy. The CT head revealed complete opacification of the right maxillary sinus and anterior ethmoidal air cells with internal foci of air without an air fluid level was

appreciated. Much like in their case, the early disease manifestation on CT scan is of mucosal thickening usually without air fluid levels.

In the present study, biopsy revealed bacterial infection in 9 (14.1%) patients. Fungal infection such as aspergillus organism was found in 5 (7.8%) patients and mucor species was found in 50 (78.1%) patients, so mucor species was more common in occurrence than aspergillus organism and bacterial infection. Moreover, Dubey et al., (Dubey et al., 2022) reported a series of 6 covid-19 patients who developed invasive pulmonary fungal infection. They reported that four of them were mucor and remaining two were of candida species. In our study, all patients had sinonasal symptoms 64 (100.0%) as shown in figure 2. Regarding palatal symptoms, eye symptoms there were 33 patients (51.56%) had palatal symptoms as shown in figure 1 and 36 patients (56.3%) had eye symptoms (eye oedema).

Additionally, Solanki et al., (Solanki et al., 2022) observed that rhino-orbital 38 (66.6%), rhino maxillary 15 (26.3%) and rhino-orbital-cerebral 4 (7.1%). Moreover, Sen et al., (SenHonavar, et al., 2021) observed that nasal ulcer/eschar, out of 2826, 1348 (48%) had nasal discharge, 1519 (54%) had ophthalmoplegia, and involvement of other cranial nerves occurred in 1459 (52%). In current study duration between covid infection and mucormycosis infection was ≤ 15 days in 17 (26.6%), more than 2weeks up to 4weeks (one month) in 45 patients (70.3%), and two months in 2 (3.1%). Also, Sen et al., (Sen, Lahane, Lahane, Parekh, & Honavar, 2021) observed that the mean duration between diagnosis of COVID-19 and development of symptoms of mucor was 15.6 ± 9.6 (3–42) days.

Moreover, Sen et al., (SenHonavar, et al., 2021) observed that most of the cases showed onset of symptoms of ROCM between day 10 and day 15 from the diagnosis of COVID-19, 56% developed within 14 days after COVID-19 diagnosis, while 44% had delayed onset beyond 14 days.

Limitations of the study

It was a single-center study, and geographical localization of cases the results may differ elsewhere. The data includes only those cases that were submitted for the study and may not be representative of the actual incidence of COVID-19-associated CAM in Egypt. The follow up of patients is limited and majority are still under active treatment.

Conclusions

The incidence of mucormycosis is likely to rise, both as a co-infection and as a sequela of COVID-19. Early diagnosis and management with appropriate and aggressive antifungals and surgical debridement can improve survival.

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Tables

Table (I): Demographic data and clinical signs of the studied patients (n = 64)

		N=64
Age (years)		54.89 ± 9.80
Sex	Male	23 (35.9%)
	Female	41 (64.1%)
Hypertension		41 (64.1%)
Covid	Active and post Covid	64 (100.0%)
Cardiac comorbidity	Free	54 (84.4%)

	Cardiac comorbidity	10 (15.6%)
Internal comorbidity	Free	57 (89.1%)
	Renal	5 (7.8%)
	Hepatic	2 (3.1%)

Data are presented as mean $\pm$ SD or frequency (%).

Table (II): Computerized tomography scan and biopsy of the studied patients

		N= 64
CT	Unilateral opacity	42 (65.6%)
	Bilateral opacity	22 (34.4%)
Biopsy	Bacterial	9 (14.1%)
	Fungal	Aspergillus 5 (7.8%)
		Mucor 50 (78.1%)

Data are presented as frequency (%). CT: computerized tomography

Table (III): Symptoms Eye, and clinical and duration between covid and mucor of the studied patients

	N= 64
Palatal symptoms	33 (51.56%)
Eye symptoms	36 (56.3%)
Duration between covid and mucor	≤ 15 days 17 (26.6%)
	More than 2 weeks up-to 4weeks 45 (70.3%)
	2 months 2 (3.1%)

Data are presented as frequency (%).



Figure (I): Blackish discoloration of the palate

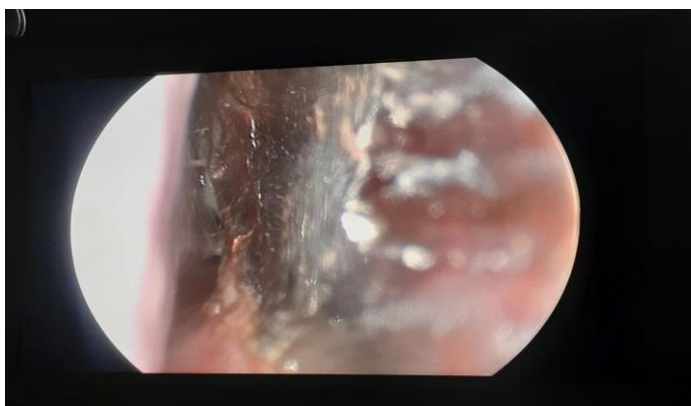


Figure (II): Nasal endoscopy showing blackish discoloration of the middle turbinate

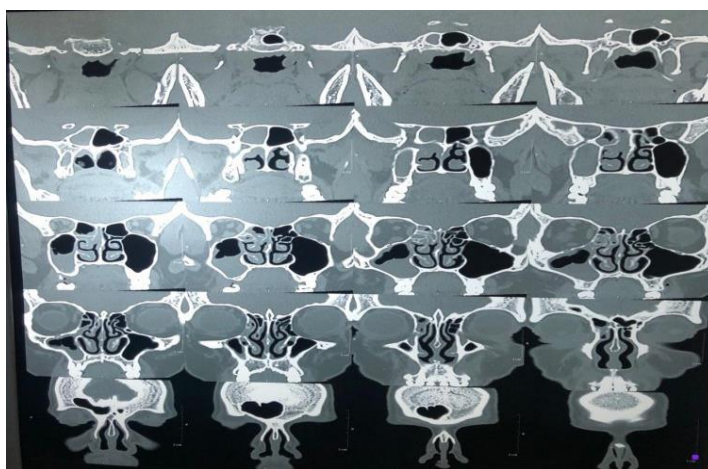


Figure (III): CT nose and paranasal sinuses showing right maxillary, ethmoidal and sphenoidal opacity.