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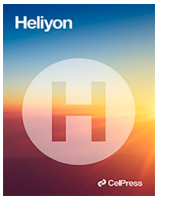

Case report

Simultaneous endobronchial and mediastinal mucormycosis in a patient with Diabetes Mellitus and SARS-CoV-2: A case report and literature review

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ABSTRACT

Background: Mucormycosis can be lethal in people with immunocompromising conditions, especially Diabetes Mellitus. Correction of the underlying disorders, instant initiation of antifungal therapy, and surgical resection are the main components of treatment. Herin, we present the successful medical management of Mucormycosis in a patient with Diabetic Ketoacidosis and positive SARS-CoV-2 test who presented with a less seen condition: the simultaneity of mediastinal mass on one side and an endobronchial mass on the other.

Case presentation: An 18-year-old male with a history of insulin-dependent DM from 4 years ago presented to our hospital with sudden onset dyspnea, chest pain, sore throat, hoarseness, cough, and sputum. Also, we detected unilateral swelling in the neck and multiple lymph nodes in the neck. Lung auscultation revealed bilateral generalized wheezing. Primary laboratory tests detected high blood sugar, metabolic acidosis, positive urine ketone, high ESR, positive CRP, and leukocytosis; his polymerase chain reaction (PCR) for SARS-CoV-2 was positive. Chest X-ray showed left upper lobe consolidation. Computed tomography scan (CT-scan) of the chest revealed a large collapse consolidation in the left lung, mild left side pleural effusion, mediastinal lymphadenopathy, and distention in the esophagus. With suspicion of malignancy, we performed flexible bronchoscopy and endobronchial Ultrasound (EBUS) which revealed a creamy tumoral lesion in the right main bronchus. The biopsy was consistent with Mucormycosis. We successfully treated Mucormycosis with Amphotericin-B liposomal.

Conclusion: Mucormycosis can mimic the clinical characteristics of malignancy, and emphasize the importance of considering appropriate differential diagnoses because timely diagnosis and treatment is potentially life-saving in Mucormycosis.

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1. Introduction

Mucormycosis is an opportunistic infection with high mortality – from 40 % to 80 % - and morbidity [1]. Immunocompromising conditions, especially Diabetes Mellitus (DM), are the main associated risk factors [2]. After the Covid-19 pandemic, we have been witnessing a rising trend in the number of Mucormycosis cases throughout the world [3,4]. Correcting the underlying disorders, instant initiation of antifungal therapy, and surgical resection are the main components of treatment [5]. Involvement of rhino-orbital-cerebral and pulmonary regions is common [6].

Mucormycosis can rarely present with mediastinal masses. In approaching this manifestation, we should always consider malignancies, especially Lymphoma [7]; hence the importance of histopathological study is clear.

Herein, we report a less mentioned presentation in the literature in a patient with Diabetic Ketoacidosis and positive SARS-CoV-2 test: the simultaneity of a mediastinal mass on one side and an endobronchial mass on the other.

2. Case presentation

An 18-year-old male with a history of insulin-dependent DM from 4 years ago, began experiencing sudden onset dyspnea and sore throat 12 days before admission. He was admitted to a local hospital with progressive dyspnea and the investigation showed high blood sugar, metabolic acidosis, and positive urine ketone. His chest X-ray showed left upper lobe consolidation. He was referred to our hospital with impressions of pneumonia and Diabetic Ketoacidosis (DKA).

At the time of admission, he was complaining of chest pain, sore throat, hoarseness, cough, and sputum; he was tachycardic (120 beats/minute), but his temperature (37.1°C), room-air O_2 saturation (97 %), and blood pressure (120/80 mmHg) were normal. He had no respiratory distress. There was no previous history of any pulmonary disease. He was not a smoker or an opium addict. His family history was negative for any acute or chronic disease.

There was unilateral swelling in the neck. Several tender and mobile lymph nodes were palpable in the anterior and posterior cervical chains on the right side. Lung auscultation revealed bilateral generalized wheezing, but heart sounds were normal. Other examinations were unremarkable.

Primary laboratory tests detected high blood sugar, metabolic acidosis, positive urine ketone, high ESR, positive CRP and leukocytosis; his polymerase chain reaction (PCR) for SARS-CoV-2 was positive (Table 1).

Echocardiography showed normal heart function - left ventricular ejection fraction of 55 % and a mean pulmonary artery pressure of 25 mmHg; we also observed no filling defect in computed tomography pulmonary angiography (CTPA) and ruled out Pulmonary thromboembolism (PTE) (Fig. 1; A1, A2, A3).

We started the treatment for DKA, and DKA resolution was obtained. Along with conservative therapy, the patient received antibiotics (meropenem 1 gr every 8 hours, vancomycin 1 gr every 12 hours) and dexamethasone 4 mg every 12 hours.

Computed tomography scan (CT-scan) of the chest revealed a large collapse consolidation in the left lung (Fig. 1; B) mild left side pleural effusion, mediastinal lymphadenopathy, distention in the esophagus (Fig. 1; C1, C2); CT-scan of the neck showed anterior and posterior cervical chain lymphadenopathy and CT-scan of paranasal sinuses was normal (Fig. 1; D).

Due to mediastinal lymphadenopathy and suspicion of malignancy, we decided to perform flexible bronchoscopy and endobronchial Ultrasound (EBUS): bronchoscopy revealed a creamy tumoral lesion in the right main bronchus (RMB), and we took a Bronchial biopsy (BB); EBUS detected some lymph nodes in the subcarinal region, transbronchial needle aspiration (TBNA) and Bronchoalveolar lavage (BAL) were done. Histopathological studies of specimens from BB and TBNA were consistent with Mucormycosis; BAL did not reveal any specific infection or malignant cells (Fig. 1; E1, E2).

Instantly, we started Amphotericin-B liposomal 5 mg/kg/day; alongside antifungal therapy, we consulted with cardiothoracic

Table 1
Laboratory results.

Lab test		Value	Unit
BS		**430**	mg/dL
VBG	PH	**7.17**	
	PCO_2	**52.8**	mmHg
	HCO_3	**14**	mmol/L
Urine ketone		**1+**	
ESR		**110**	mm/hour
CRP		**2+**	
procalcitonin		0.08	ng/ml
CBC	White blood cells	**19.5**	thousands/uL
	Hemoglobin	13	g/dL
	Platelets	564	thousands/mL
PCR for covid-19		**Positive**	
Blood culture		No growth	
Urine culture		No growth	

Bold values imply significant results.
BS, blood sugar; VBG, venous blood gas; PCO_2, partial pressure of carbon dioxide; HCO_3, bicarbonate; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; CBC, complete blood count; PCR, polymerase chain reaction.

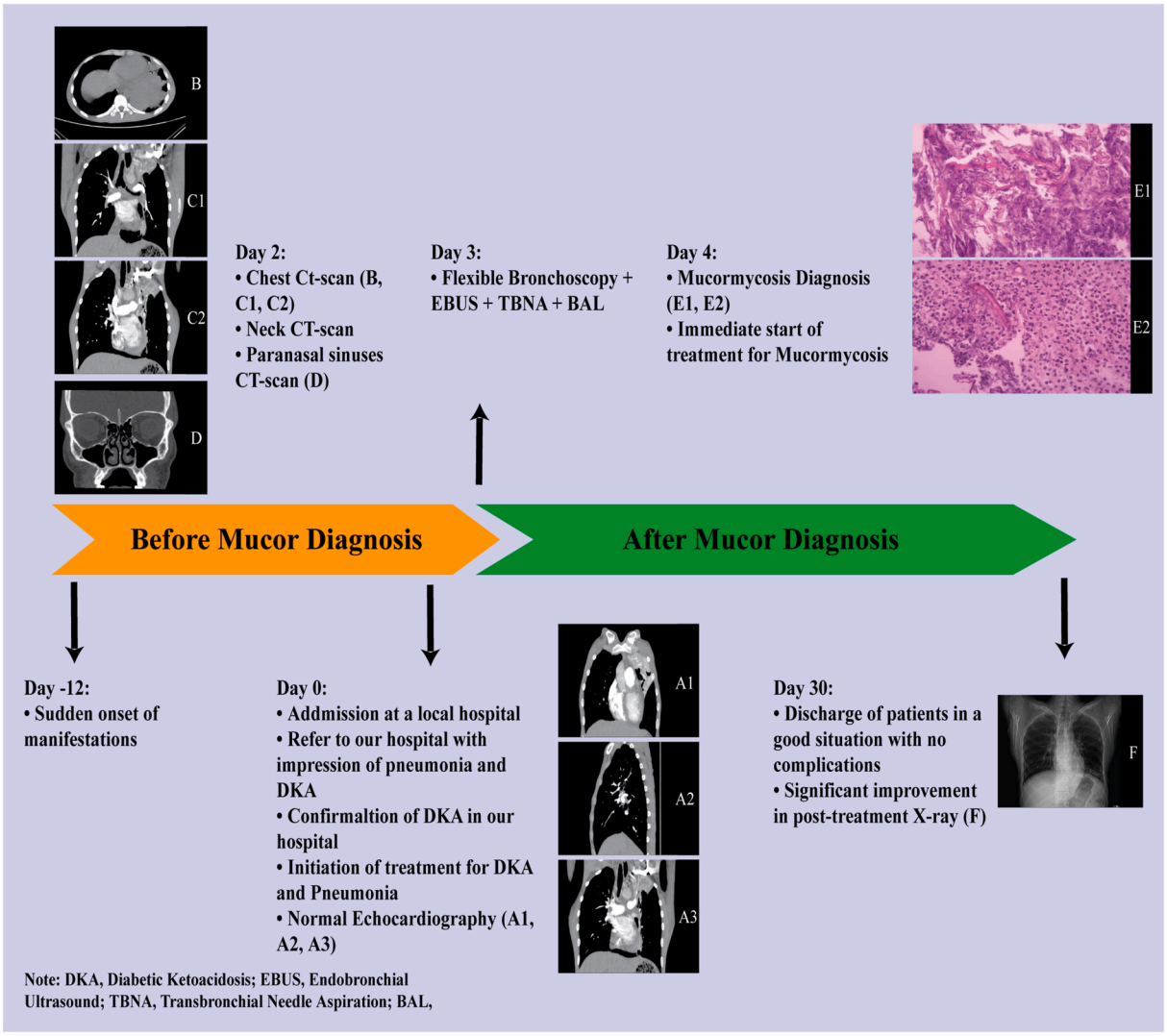

Fig. 1. Timeline of the events before and after hospitalization of the patient; (A1, A2, A3) CTPA showing no filing defect; (B) CT-scan of the chest showing a large collapse consolidation in the left lung; (C1, C2) CT-scan of the Chest showing the compression effect on the Esophagus; (D) Ct-scan of the paranasal sinuses showing no involvement; (E1, E2) Histopathology specimens from the case shows abnormal tissue, dense infiltration of inflammatory cells and necrotic materials; fungal elements including wide branching hyphae and spores can also be seen without septation; (F) Chest X-ray of one month; no evidence of previous left upper lobe consolidation and pleural effusion; mediastinal lymph nodes have been also reduced in size.

surgeons for a surgical approach and they disagreed with the surgery because of inoperability.

Due to continued hoarseness, otolaryngologists performed a Stroboscopy that was normal; they recommended continuing treatment with Amphotericin-B liposomal. Treatment continued for one month. The patient had good compliance with the treatment, improved gradually, and was discharged from the hospital in a good situation and with no complications. His post-treatment chest X-ray showed significant improvement (Fig. 1; F).

3. Discussion

Multiple pathologies can mimic the manifestations of mediastinal mucormycosis such as lymphoma, thymoma, thyroid mass, lung carcinoma, sarcoidosis, and teratoma. Our patient's characteristics including history and physical examination and the mediastinal lymphadenopathy led us to the primary diagnosis of malignancy, but further investigations via performing flexible bronchoscopy and EBUS and evaluating the taken biopsy revealed Mucormycosis.

Mucor involvement is categorized into six groups based on anatomic location: Rhino-orbital-cerebral (most common), pulmonary, cutaneous and soft tissue, disseminated, gastrointestinal, and other sites involved include joints, bone, peritoneum, and heart (rare)

Table 2
Review of the related literature.

Autor/year	Patient's Characteristics	Clinical & Paraclinical Manifestations	Bronchoscopy	Treatment	Outcome
Vyas et al. [25]/2014	30 Y.O/M/Negative history of any disease, smoking, Tobacco and Alcohol consumption.	Bilateral neck swelling, non-productive cough, exertional dyspnea, hoarseness, weight loss, cervical LAP, engorged umbilical veins in the left side of the chest and upper abdomen, diminished breath sounds over the right infraclavicular region with crackles. Chest X-ray: an abnormal opacity in the right superior mediastinum with mediastinal widening/Chest CT-scan: a large infiltrative soft tissue mass in anterior, middle, posterior and superior mediastinal compartments with displacement and compression of SVC and great vessels of the arch, bilateral hilar LAP, few nodular lesions in the RUL and RML with involvement of adjacent pericardium/Supraclavicular lymph node biopsy: granulomatous lymphadenitis, septate branching hyphae suggestive of Zygomycete/Upper gastrointestinal endoscopy: an extrinsic compression due to a large mass anterior to the Esophagus/Endoscopic ultrasound-guided FNAC: a granulomatous lesion consistent with Zygomycete.	Extensive compression along the right lateral and anterior wall of the lower trachea with areas of yellowish cheesy material at the indentation site/Bronchial wash examination did not show any infection or malignant cells.	Antibiotic therapy (Meropenem), antifungal therapy (Amphotericin-B).	Death.
NG et al. [26]/202	31 Y.O/F/Housewife/seven weeks pregnant/Negative history of any disease, recent traveling, contact with animals and smoking.	Chronic cough of one month, loss of weight, loss of appetite, occasional hemoptysis, reduced breath sounds on the left lung, deviation of trachea to the left. Negative blood and sputum cultures, including Mycobacterium and sputum fungal culture/CRP: 14.5 mg/L, ESR: 65 mm/h/Chest X-ray: left-sided homogenous opacity, tracheal deviation to the left side/ Ultrasound: collapsed left lung/ Chest CT-scan: left hilar mass with infiltration into the left main bronchus, mediastinal LAP/ Endobronchial biopsy: inflamed tissue with the presence of fungal organism, no granuloma and malignancy/Fungal PCR: Rhizopus microspores.	Flexible bronchoscopy: a whitish endobronchial mass completely occluding the LMB, about 2 cm from the carina/Rigid bronchoscopy: Endobronchial snaring, observed copious amounts of secretions along distal airways of the LUL and LLL, unhealthy mucosa, multiple nodules.	Bronchoscopic intervention and intravenous Amphotericin-B.	Complete resolution in the chest X-ray, 2 weeks after treatment.

Y.O., Year Old; M, Male; F, Female; LAP, Lymphadenopathy; SVC, Superior Vena Cava; RUL, Right Upper Lobe; RML, Right Middle Lobe; FNAC, Fine Needle Aspiration Cytology; CRP, C-Reactive Protein; ESR, Erythrocyte Sedimentation Rate; PCR, Polymerase Chain Reaction; LMB, Left Main Bronchus; LUL, Left Upper Lobe; LLL, Left Lower Lobe.

[6]. Pulmonary Mucormycosis has nonspecific clinical manifestations, but dyspnea, chest pain, and hemoptysis are the main ones and its radiologic clues are more helpful. Pleural effusion, nodules, consolidation, and ground glass opacities are the most common findings; we also have the halo sign, reverse halo sign, air crescent sign, and hypodense sign (the last two are less specific) [8–10]. In our patient, dyspnea and chest pain – without hemoptysis – were the main complaints, and large collapse consolidation and mild pleural effusion in the left lung and mediastinal lymphadenopathy were the radiological signs, and they all hind in follow up studies.

Flexible bronchoscopy is considered a safe and useful procedure in diagnosing Mucormycosis. A study performed by Muthu et al. [11] reported that out of 66.7 % of their pulmonary Mucormycosis flexible bronchoscopy were abnormal. Adherent mucus plug (33.3

%), purulent secretions (29.6 %), and endobronchial nodule or growth (4.9 %) were the most common findings. In our study, flexible bronchoscopy and EBUS revealed creamy tumoral lesion in the RMB and some lymph nodes in the subcarinal region, respectively.

Mucormycosis has a tendency to involve patients with DM and Covid-19, and our patient had both of these conditions. Hyperglycemia and acidosis interrupt phagocytic killing and chemotaxis as the essential components of defending against this infection [6]. Studies suggest the combination of multiple factors like high background prevalence of Mucormycosis in underdeveloped countries, immune dysfunction in covid-19 and related therapies like steroids and uncontrolled or undiagnosed DM as the reason. They believe that careful use of immunosuppressive therapies like steroids and aggressive control of glucose level are the main ways of confrontation [3,4,12]. Our first therapeutic approach was the treatment of Covid-19 and correcting hyperglycemia and acidosis which substantially helped with the final resolution of the disease.

Mucormycosis is a rare disease with high morbidity and mortality, and the diagnosis can be challenging, thus paying attention to regional prevalence, and practical guidelines can be of high value. The prevalence of Mucormycosis is high in Asia, and India has the highest prevalence (≈0.14 cases per 1000 population), which is 80 times the prevalence of Mucormycosis in developed countries [13,14]. In a study, Iran, where we practice medicine, had the most reported cases (74 cases) in the Middle East and North Africa (MENA) region [15]. Two studies have reported the prevalence of different infection sites, and in both pulmonary Mucormycosis had the second highest prevalence with 9.2 % [16] and 5.2 % [17] of all Mucormycosis cases.

Global guideline for the diagnosis and management of mucormycosis [1] is a valuable resource for the diagnosis and management of Mucormycosis.

This guideline highly encourages physicians to initiate medical and surgical interventions due to the often rapidly progressive and destructive nature of the infection. This guideline highly recommends appropriate imaging followed by surgical intervention. In our patient, we utilized multiple imaging modalities including chest X-ray, CTPA, and CT-scan of the chest, neck, and paranasal sinuses. Additionally, we consulted with cardiothoracic surgeons for a probable surgical intervention. But it was denied due to inoperability.

Global guideline for the diagnosis and management of mucormycosis suggests that first-line treatment is with high-dose Amphotericin-B liposomal, but discourages using Amphotericin B deoxycholate, because of its severe toxicity. We used Amphotericin-B liposomal 5 mg/kg/day which is in line with this guideline.

One issue we faced was using Corticosteroids. Although Corticosteroids can be helpful in hospitalized COVID-19 patients [18,19], the simultaneity of Covid-19 with DKA and Mucormycosis made its application challenging. Regarding the DKA and dexamethasone effects on glycemic control, we managed this problem by close monitoring of the patient and his laboratory values including blood sugar, venous blood gas, and urine ketone. In terms of Mucormycosis and immunosuppressive effects of dexamethasone, one solution that helped us was paying close attention to the clinical condition of the patient, as our patient improved dramatically with administrating Amphotericin-B liposomal. Treating patients with multiple simultaneous disorders needs extensive consideration, and we believe there is a need for studies to better clarify this issue.

Previous studies reported rare cases of Mucormycosis with endobronchial [20–22] and mediastinal [23,24] involvements. Our patient presented with a less seen situation: the simultaneity of a mediastinal mass on one side and an endobronchial mass on the other, and this co-occurrence and the patient's characteristics, especially mediastinal lymphadenopathy led to primary misdiagnosis of malignancy. To the best of our knowledge, only two authors have reported the same situation: Vyas et al. [25] and Ng et al. [26]. They both mentioned malignancy as their main differential diagnosis (Vyas et al. due to cervical and mediastinal lymphadenopathy, Ng et al. due to aggressive properties of the mass), but histopathology revealed the diagnosis of Mucormycosis (Table 2).

4. Conclusion

Mucormycosis is a fatal disease with the ability to mimic the manifestations of malignancy (lymphoma in particular); considering appropriate differential diagnoses and immediate initiation of treatment after suspicion are potentially life-saving, especially in immunocompromised patients.

5. Patient perspective

The patient stated that he was thankful for the life-saving treatment he received. He was particularly happy because of receiving non-surgical treatments.

Ethics and consent

Written consent was obtained from the patient regarding publishing all images, clinical data, and other data included in the manuscript with the journal's patient consent policy before starting the work. Also, this study conforms to the Declaration of Helsinki.

Data availability statement

Data associated with our study has not been deposited into a publicly available repository and data will be made available on request via the corresponding author.

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Conflict of interest disclosure

The authors have no conflict of interest.

CRediT authorship contribution statement

Amin Sayyadi: Writing – review & editing, Writing – original draft, Software, Data curation. **Faranak Salajegheh:** Writing – review & editing, Conceptualization. **Behnam Dalfardi:** Writing – review & editing, Supervision. **Mohsen Shafiepour:** Writing – review & editing, Supervision, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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