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PULMONARY MUCORMYCOSIS; CHALLENGES IN DIAGNOSIS AND TREATMENT

Respiratory Medicine

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ABSTRACT

Pulmonary mucormycosis is an angio-invasive fungal infection by mucorales with high mortality and morbidity. This pulmonary infection is caused by inhalation of spores and seen mostly in immunocompromised patients. In TB endemic country like India, pulmonary mucormycosis pose a diagnostic dilemma due to similar clinical presentation. Our 49-year-old female patient presented with characteristic symptoms and started on anti TB drugs. As patient was not having symptomatic relief, patient was investigated. On bronchoscopy, fungal mass seen and biopsy of which shown organisms consistent with mucormycosis. Patient underwent lobectomy and received 5 months of antifungal treatment.

KEYWORDS

INTRODUCTION;

Mucormycosis is an emerging, life threatening and angio- invasive fungal infection caused by order Mucorales subphylum Mucormycotina (Hibbet, Bindal, & Bischoff, 2007). Rhizopus spp., Mucor spp., and Lichtheimia spp are most common agents of mucormycosis. Rhizomucor,saksenaea, cunninghamella and apophysomyces are less common genera of mucorales causing infection (Petrikkos, et al., 2012). Infection is caused by inhalation of sporangiospores, inoculation of wounds or ingestion (Serris, Danion, & Lanternier, 2019)

Clinically it can be presented as rhino cerebral, pulmonary, cutaneous, gastrointestinal or other forms including rare forms such as endocarditis, osteomyelitis, peritonitis, renal etc. (Petrikkos, et al., 2012) (Skiada, Pavleas, & Drogari- Apiranthitou, 2020)

Conditions that predispose to mucormycosis include diabetes mellitus, hematological malignancies, other malignancies, transplantation, neutropenia, steroid therapy, trauma, iron overload, intravenous drug use and malnourishment. This disease is seen in immunocompetent individuals when fungal spores directly inoculated in skin after trauma or burns. (Skiada, Pavleas, & Drogari- Apiranthitou, 2020) (Petrikkos, et al., 2012) (Prakash & Chakrabarti, 2019) Most common risk factor for mucormycosis in the world is uncontrolled type 2 diabetes mellitus. (Skiada, Pavleas, & Drogari- Apiranthitou, 2020) Pulmonary mucormycosis is a rare presentation in diabetic patients associated with high mortality and morbidity

Case Report:

A 49-year-old female presented to nearby hospital in native place complaining of cough with mucoid expectoration, grade II mMMRC breathlessness, intermittent low grade fever spikes, right sided pleuritic type of chest pain, loss of appetite and loss of weight for 2 months in August 2021. No history of tuberculosis or contact with tuberculosis is present. No history of any illness, hospitalizations or addictions in past

Her blood routine examination revealed Hb-11.0 gm/dl, total leucocyte counts of 10,900/ cmm with 67% neutrophil, 28% lymphocytes 3% eosinophils. Renal function tests and liver function test were within normal limits. Patient diagnosed of diabetes mellitus (HbA_1C: 8.21) and started on oral hypoglycemic agents.

Viral markers were negative. Thoracocentesis was showing reddish turbid, exudative fluid with sugar of 116.8 mg% and total WBC count of 3600/mm^3 (90% polymorphs and 10 % lymphocytes). ADA was 660U/ML. Mantouex test done with 0.1 ml of PPD of 10 u shown induration of 18 mm and erythema of 22 mm. sputum AFB mucoid negative

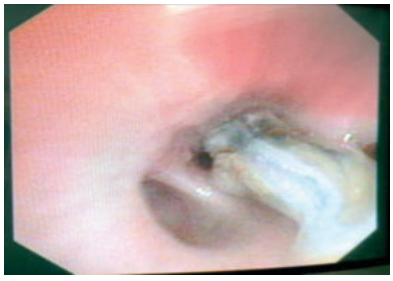

Figure 1: bronchoscopy imaging showing right lower lobe bronchus filled with fungal mass

CECT Thorax revealed large areas of heterogeneous consolidation in right lower lobe with non-enhancing component (abscess in evolution) with adjacent patchy parenchymal opacities and few enlarged mediastinal lymph nodes and Most likely to be sequel of infective pathology ?tuberculosis with pneumonitis. Patient received a course of oral antibiotics and was initiated on anti-TB treatment.

In December 2021, patient got referred to our hospital with no relief of symptoms after 4 months of anti-TB treatment and blood tinging of sputum and HRCT thorax report showing irregular cavitatory lesion of 5.4 X4.4 cm showing fluid level with irregular margins in superior and lateral basal segments of right lower lobe and fibro bronchiectasis and fibrocavitatory lesions, bronchial wall thickening around it

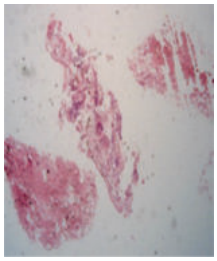

Figure 3: H&E Staining of Biopsy of Bronchoscopic lesion

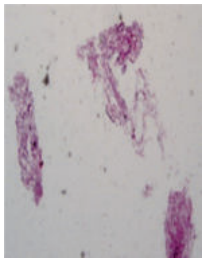

Figure 3: PAS Staining of Biopsy of Bronchoscopic lesion

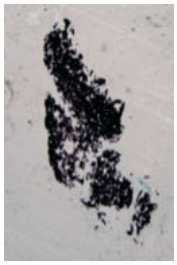

Figure 4: GMS Staining of Biopsy of Bronchoscopic lesion

On examination, she had fair general condition, afebrile, pulse rate of 94/min, respiratory rate of 18/min, blood pressure of 120/70 mmHg, SpO2 of 98%, respiratory system examination revealed vesicular breath sounds present bilateral with intensity absent in right infrascapular area. Other systemic examination within normal limits.

Her blood routine examination shown Hb of 11.3 gm/dl, total leucocyte counts of 11,500/cmm with 71% neutrophils and 21% lymphocytes. platelet count of 2.1 lakh/cmm. Renal function test and liver function test within normal limits. sputum CBnaat Mtb not detected. Sputum and blood culture sterile

Patient treated with injections of piperacillin-tazobactam and metronidazole for 10 days along with supportive management

CECT thorax done on 29 December 2021 showed a cavitatory lesion with air fluid level of 3.8X4.2X3.1 cm in lateral basal segment of right lower lobe communicating with lateral segmental bronchus with encysted pleural effusion of 4.4X1.6 cm. Centrilobular nodules with tree in bud appearance in superior segment of right lower lobe suggestive of infectious bronchiolitis.

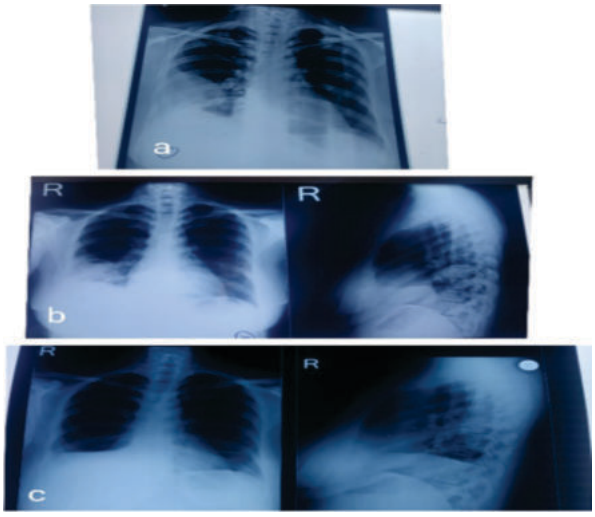

Figure 5: a chest x-ray pa view showing heterogeneous opacity involving right lower zone. b. chest x-ray PA view showing thick walled cavity with air fluid level within. c. Post-surgery chest x-ray showing clearance of lesion

Bronchoscopy showed right lower lobe bronchus obstructed with white mucus plug? fungal mass. Bronchial washing cytology shown numerous Broncho columnar cells no alveolar macrophages no evidence of epithelial histiocytic or atypical cells. Bronchial biopsy of lesion on microscopy showed only fungal organisms consistent with morphology of mucormycosis. PAS and GMS positive in fungus. Fungal culture of bronchial washing sample didn't show any fungal growth. Bronchial washing CBNaat; MTb not detected. Bronchial washing AFB culture; negative.

After preanesthetic checkup and preparation, lobectomy of right lower lobe was done followed by 14 days' course of liposomal amphoptericin B and oral posaconazole for 5 months. Patient became completely asymptomatic and Repeat CT thorax at the end of treatment revealed no recurrence of lesions.

DISCUSSION;

Pulmonary mucormycosis is a relatively uncommon but important opportunistic fungal infection in immunocompromised individuals.

Tissue necrosis resulting from angio-invasion and subsequent thrombosis is the clinical hallmark of invasive mucormycosis. Infection is rapidly progressive and results in death unless underlying risk factors are corrected ,treated aggressively with antifungal agents and surgical excision in most cases. (Petrikkos, et al., 2012) Because of increased individuals at risk and improved diagnosis, incidence of mucormycosis is increased (Bitar, et al., 2009)

In developed countries, increased number of patients is associated with hematopoietic stem cell transplant recipients and patients with hematological malignancies. (Maureen, Theoklis, & Wendy L Buchanan, 2005) In developing and tropical countries, uncontrollable diabetes mellitus is most common predisposing factor in all categories of mucormycosis except in renal. Increase in mucormycosis may be correlated with increase in diabetes patients in developing and tropical countries (Chakrabarti, Das, & Mandal, 2006) .In our case, our patient is a female with recently diagnosed diabetes mellitus. She was having an HbA1c of 8.9 when symptoms started but she didn't have an episode of ketoacidosis or blood sugar values more than 300 mg/dl. In patients of mucormycosis with diabetes, those presenting with ketoacidosis have higher rate of mortality but ketoacidosis is not an independent risk factor for mortality (Corzo-Le´on, Luis D. Chora-Hern´andez, Ana P. Rodr´ıguez-Zulueta , & Thomas J. Walsh , 2018).

Figure 6: HRCT thorax showing cavitatory lesion with air fluid level is noted in lateral basal segment of right lower lobe measuring 3.8X4.2X3.1 cm in size and seen to communicate with lateral segmental bronchus in this region. Area of consolidation is noted along inferior aspect of cavity. Surrounding areas of fibrosis with tractional bronchiectasis noted in right lower lobe. Laterally mass is seen to adjacent to an encysted pleural effusion measuring4.4X1.6 cm with thickening and enhancement of adjacent pleura

Clinical features include Prolonged fever, not responding to broad-spectrum antibiotics. Nonproductive cough is a common symptom and hemoptysis, pleuritic chest pain and dyspnea are less common symptoms. (Petrikkos, et al., 2012) Our patient had all these symptoms along with loss of weight and appetite. As an endemic country for tuberculosis, characteristic symptoms, high ADA on thoracocentesis, Positive mantouex test and radiological characteristics suggesting of tuberculosis, patient was started on antitubercular treatment from peripheral hospital. In countries like India with high prevalence of tuberculosis, there should be clinical suspicion of pulmonary mucormycosis, when they present with cavitation on chest radiograph with negative sputum AFB Smear. (Garg, Marak, Verma, & Singh, 2008) Our patient was suspected of pulmonary tuberculosis and started on treatment clinically. But patient didn't have any symptomatic relief and referred to our hospital. Patient had received adequate antibiotic therapy, investigated including bronchoscopy. In our case, bronchoscopy shown fungal growth. Pulmonary mucormycosis most commonly occur involving lung parenchyma, but can also see involving airways. (Tanriverdi, Atalay, Kart, Altuntas, & Tomruk, 2014) (Donohue, Scott, Walker, & Bromberg, 1980)

Pulmonary mucormycosis may present as mass, lobar consolidation, nodular infiltrates, cavitation and infarcts in chest radiography. Reversed halo sign (peripheral consolidation with central ground glass) may be seen in immune compromised hosts (Hammer, Madan, & Hatabu, 2018). In Our case, earlier scan shown heterogenous consolidation with a nonenhancing component within (abscess in progression) which later turned into an irregular fluid filled cavity with fibrobronchiectatic lesions surrounding it.

It is difficult to establish clinical diagnosis of mucormycosis. Due to lack of microbiological and histological proof, cases may go missed or patients has to be treated presumably. (De Pauw B, 2008) Laboratory diagnosis of mucormycosis includes histopathology, direct examination of wet mounts and culture.

histopathology can differentiate between presence of fungus as a pathogen from a culture contaminant and will show blood vessel invasion. In Mucorales typically non-pigmented, wide (5–20 μm), thin-walled, ribbon-like hyphae with no or few septations and right-angle branching are seen. (Ribes, Vanover- Sams, & Baker, 2000) Routine hematoxylin and eosin (H&E) stains may show only the cell

wall with no structures inside, or occasionally, very degenerate hyphae. Grocott methenamine-silver (GMS) and periodic acid-Schiff PAS stains will show fungal wall. (Guarner & E. Brandt, 2011) Direct Microscopy of KOH wet mounts can be used For a rapid presumptive diagnosis of mucormycosis, preferably using fluorescent brighteners such as Blankophor and Calcofluor White together with KOH, which enhance the visualization of the characteristic fungal hyphae (Walsh, Gamaletsou, McGinnis, Hayden, & Kontoyiannis , 2012). It is strongly recommended, along with histopathology, by a panel of experts of the European Confederation of Medical Mycology in cooperation with the Mycoses Study Group Education and Research Consortium (ECMM/MSG ERC) (Global guideline for the diagnosis and management of mucormycosis: an initiative of the European Confederation of Medical Mycology in cooperation with the Mycoses Study Group Education and Research Consortiu, 2019). In our case, bronchial biopsy shown fungal elements consistent with mucormycosis which was PAS and GMS positive. Histopathology of lobectomy specimen shown congestion, acute on chronic inflammation, antracotic pigment, fungal elements consistent with mucormycosis, micro abscesses, proliferation of bronchial gland showing reactive atypia.

Culture of specimens allows identification to the genus and species level, and antifungal susceptibility testing. most medically significant mucor species grow rapidly at temperatures of 37 ◦C. They grow on virtually any carbohydrate substrate, colonies appearing usually within 24–48 h and identification is based on colonial and microscopic morphology and growth temperature (Walsh, Gamaletsou, McGinnis, Hayden, & Kontoyiannis , 2012). A positive culture from a sterile site can confirm the diagnosis, while a positive culture from a non-sterile site can be due to contamination and should be correlated clinically and radiologically to make probable diagnosis (Global guideline for the diagnosis and management of mucormycosis: an initiative of the European Confederation of Medical Mycology in cooperation with the Mycoses Study Group Education and Research Consortiu, 2019). however culture can be falsely negative in up to 50% of mucormycosis cases (Walsh, Gamaletsou, McGinnis, Hayden, & Kontoyiannis , 2012). In our case, bronchial washing fungal culture was negative.

Multimodal approach including correction of predisposing factors, early initiation of antifungal therapy and removal of infected tissue is suggested for treatment of pulmonary mucormycosis. (Skiada, et al., 2018) Our patient was a case of diabetes mellitus, we have started her on insulin along with oral hypoglycemic agents and proper glycemic control ensured. ESCMID/ECMM guidelines recommends early surgical debridement whenever possible along with antifungal treatment. (Global guideline for the diagnosis and management of mucormycosis: an initiative of the European Confederation of Medical Mycology in cooperation with the Mycoses Study Group Education and Research Consortiu, 2019) Our case had lesions localized to right lower lobe, hence after preanesthetic clearance, patient undergone right lower lobe lobectomy. ESCMID/ECMM strongly recommends use of liposomal amphoptericin B 5-10 mg/kg as first line therapy and moderately supports use of isavuconazole and posaconazole. There is no evidence regarding duration of therapy. ESCMID/ECMM suggests continuation of therapy till immune suppression is reversed, signs and symptoms of disease improved and good response seen radiologically. Intravenous therapy is moderately supported in stable disease and oral switching to isavuconazole and posaconazole can be done. (Global guideline for the diagnosis and management of mucormycosis: an initiative of the European Confederation of Medical Mycology in cooperation with the Mycoses Study Group Education and Research Consortiu, 2019).Our patent received 2 weeks of intravenous liposomal amphoptericin B and then switched to oral therapy with posaconazole for 5 months

CONCLUSION

Pulmonary mucormycosis is an uncommon life threatening infection seen in immunocompromised individuals. Uncontrolled diabetes is the most common risk factor in developing countries. As a TB endemic country, with similar clinical features at presentation, clinicians should have a clinical suspicion of pulmonary mucormycosis for timely management. Multimodality treatment including surgical resection whenever possible, adequate antifungal treatment and correction of immunosuppression are keys to successful treatment.

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