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FUNGAL PNEUMONIA WITH REVIEW OF LITERATURE ON CANDIDA – A SILENT KILLER IN CRITICAL CARE PATIENTS.

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INTRODUCTION: Pulmonary fungal infection appears to be an important problem in patients with respiratory diseases especially in patients who are admitted to the medical respiratory ICU. Several host characteristics, such as a very high incidence of pulmonary tuberculosis (PTB) [1], malignancies, chronic pulmonary obstructive disease (COPD) [2], and others, also contribute to a high predilection for fungal diseases in the Indian population. Many outbreaks of different fungal infections have been periodically reported from different parts of India, including Candida auris [3] and, more recently, COVID-19-associated mucormycosis [4,5].

Fungal infections are neglected most of the time, may be due to our less resources to diagnose or we are from a country with maximum TB burden. Most of the time we start the patients on Anti

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tubercular drugs based on clinic-radiological basis without investigating the patients to rule out fungal infections but fungal infections must to be ruled out as many articles supports that fungal infections are a silent killer in many long standing bacterial infections as a super added infections or a new infection in a immunosuppresed patients.

The incidence of fungal pneumonia is rising with the increasing use of immunosuppressants, inadvertent use of antimicrobials, newer diagnostic modalities, and increased survival of immunodeficient patients [6]. The common organisms that cause fungal pneumonia are Aspergillus, Cryptococcus, Mucor, and Pneumocystis jirovecii [7,8].

Despite encompassing more than two-thirds of cases of fungal infections, invasive candidiasis rarely manifests as Candida pneumonia. Invasive candidiasis is defined as the presence of Candida in the blood (candidemia) or deep-seated Candida infections such as intra-abdominal abscess, osteomyelitis, or renal abscess [9]. The presence of Candida isolated from respiratory specimens is usually regarded as colonization. The diagnosis of Candida pneumonia is difficult due to the nonspecific clinical and radiological features and the lack of specific biomarkers which necessitates the histopathological demonstration of the organism for confirmation of diagnosis. The rarity of Candida pneumonia makes the existence of this entity a matter of ongoing debate. In this review, we highlight the current evidence regarding the existence of Candida pneumonia and discuss the pros and cons of antifungal therapy (10, 11).

The true incidence of Candida pneumonia ranges from 0.23% to 0.4% [10,11].

Among different respiratory diseases, COPD is the most common disease among patients at risk of pulmonary fungal infection. DM is the most common comorbid disease associated with high fungal recovery rates especially Candida. (12)

ABSTRACT: Here we discuss about 3 cases of fungal pneumonia in a respiratory critical care unit with an update on review of literature. Diagnosis and treatment of the same has been discussed.

STUDY DESIGN: case series with review of literature

PLACE OF STUDY: SEPM – NSCB government hospital, Jabalpur, MP.

CASES DESCRIPTION:

CASE 1 :

A 15 YEAR, young male coming from central India, presents with complaints of fever, cough with expectoration and loss of appetite for 1 month. He was diagnosed with type 1 diabetes mellitus for 2 years and was on insulin therapy irregularly. No history of tuberculosis or COVID 19 infection in the past. He was initially treated by private doctors many a times for the same complaints on OPD basis. Patient was started on empirical antibiotics and other supportive managements were started.

He was taken for battery of investigations, of which – CBC showed sepsis and anaemia, sputum AFB and CBNAAT was negative. Chest x ray showed heterogenous infiltrates in right mid and lower zone and left lower zone (dense infiltrates). Blood, sputum and urine cultures showed no growth. Beta D Glucan was raised (nonspecific).

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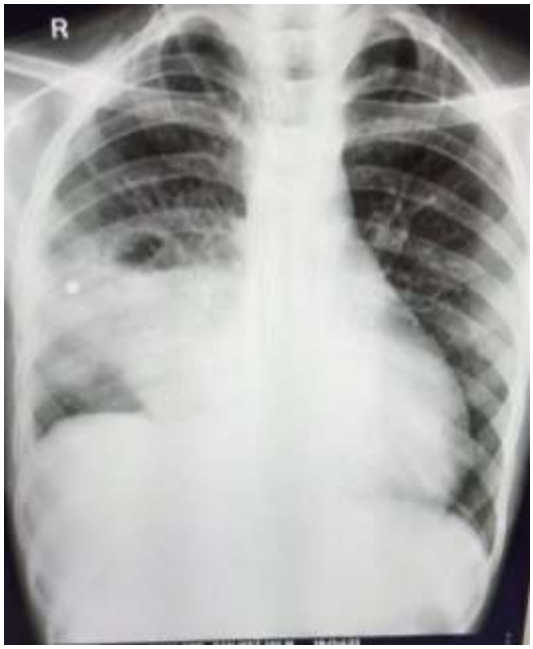

Picture 1 – chest x ray shows dense cavitary consolidation of right mid and lower zone

Patient was taken for bronchoscopy and samples were taken. BAL – AFB AND CBNAAT were inconclusive. Bronchial biopsy showed fungal hyphae with inflammatory cells.

After diagnosis, patient was started on Tab. Itraconazole 400 mg BD with INSULIN therapy to control his blood glucose level. Patient improved dramatically with antifungal treatment.

CASE 2:

A 30-year male, hailing from central India, presents to us with complaints of difficulty in breathing, fever, cough with expectoration and loss of appetite for 3 to 4 months. He was started on anti-tubercular drugs on clinic-radiological basis elsewhere before 2 months, but he showed no improvement. No history of any other comorbidities in the past or covid infection in the past.

On examination, pulse was 140/min , respiratory rate was 30/min, BP was 130/76 mmhg, saturation levels were 94% at Room air. Patient had pallor with bilateral coarse crepts in the basal lung fields. Symptomatic management was then started in the form of empirical antibiotics with IV hydrocortisone, IVfluids were given with along with BiPAP support.

Blood investigations revealed anaemia with hypoproteinaemia. Chest radiology showed bilateral diffuse infiltrates. Sputum AFB & CBNAAT were negative. All cultures were negative. USG abdomen and pelvis was normal. Beta D Glucan (BDG) was raised (nonspecific). Urine routine microscopy was normal. Patient was subjected to bronchoscopy and BAL reports were inconclusive. BAL – AFB & CBNAAT were negative. BAL cytology was negative. Bronchial biopsy from mucosal irregularity showed Fungal hyphae with necrosis. Hence patient was started on Tab fluconazole 400 mg BD and he was discharged on clinical improvement.

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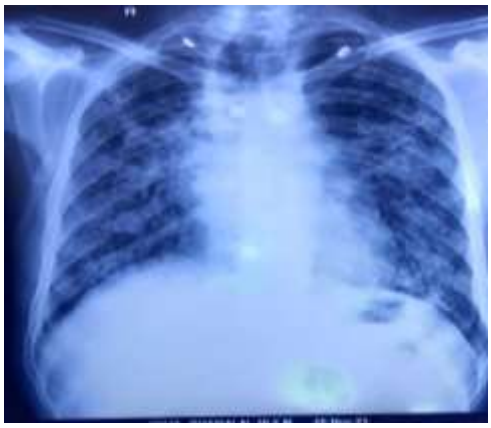
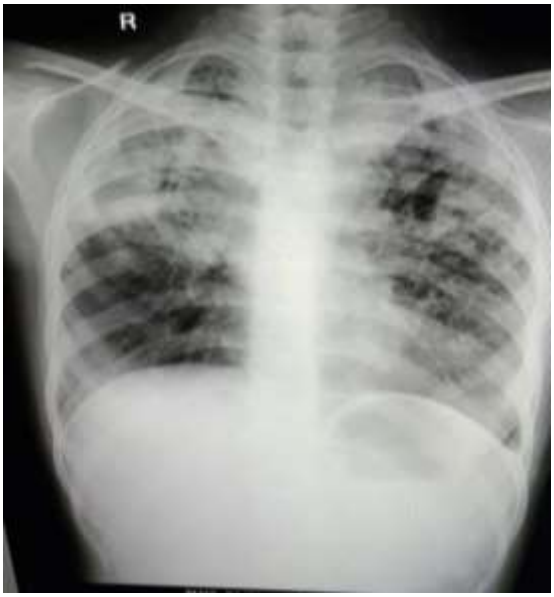


Picture 2 – shows bilateral diffuse consolidation (right > left) with tracheal shift to right side.

CASE 3: A 69 year old Male , coming from central India , came with the complaints of shortness of breath with altered sensorium since one day, fever and cough with expectoration for 1 to 2 months. Patient was a known case of COPD and was on irregular inhaler usage. On examination, patient was tachypnoeic, hypoxic and hypotensive. Patient was admitted in critical care and was intubated. Patient was started on empirical antibiotics and blood samples were sent fo cultures before antibiotic shot. Other supportive measurements were given.

Blood reports revealed sepsis, chest radiography showed right lower zone cavitary consolidation. Cultures were negative. Beta D Glucan was raised (nonspecific). Patient was subjected for bed side bronchoscopy with proper consent and strict aseptic precautions. BAL samples were normal but biopsy from the right lower lobe mucosa which showed irregularity came out to be positive for hyphae with increased inflammatory cells in the histopathology report.

Patient was then started on IV fluconazole, following which patient showed drastic improvement in his health condition and patient was extubated on Day 4.



Picture 3 shows bilateral emphysematous lung with increased vascular markings in bilateral hilar regions with increased haziness in the left lower zone.

REVIEW OF LITERATURE: Diabetes mellitus is a predisposing factor of oral candidiasis (opportunistic infection caused by overgrowth of commensal of the mouth - Candida species e.g.,

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the most prevalent Candida albicans), especially of pseudomembranous candidiasis (13,14). Also non-albicans species (Pichia, Trichosporon, Geotichum) can be identified in the oral cavity of patient with poorly controlled diabetes, being prone to frequent and severe fungal infections (15,16).

A study by Schnabel et al. [17] highlighted this subject with an attempt to identify the incidence of Candida pneumonia in critically ill patients. They analyzed 701 BAL samples and described Candida as an etiology of pneumonia in only 5 patients (0.7%). Out of these 5 patients, only 1 was immunocompetent. Another prospective study described the true incidence of Candida pneumonia in nonneutropenic critically ill patients, which was 8% [18], although Candida isolation from the biopsy sample was 40% in this report. The existence of Candida pneumonia is also debated by Meersseman et al. [19] who did not find a single proven case in patients with the identification of Candida in histopathology. Despite the high incidence of Candida isolation (40–56%) in respiratory samples (BAL and sputum) in all aforementioned studies, true Candida pneumonia remains a rare entity [19].

Candida spp. as a causative agent of VAP is controversial. Some authors exclude it as an etiological agent and others estimate its incidence below 1%, related to risk factors such as severe immunosuppression, malnutrition, high fungal load (e.g., diabetes, alcoholism, gastroesophageal reflux, presence of esophageal diverticula), or broad-spectrum antibiotic therapy [20].

The role of serological assay like beta-D-glucan (BDG) in invasive candidiasis was analyzed by Su et al. [21]. According to their report, endotracheal aspirate and BAL BDG were better predictors of suspected pulmonary candidiasis in comparison with serum BDG. Measuring serum BDG has no value in predicting pulmonary Candida infections, particularly in the absence of concurrent candidemia. However, BDG can be positive in other fungal infections too (Aspergillus and P. jirovecii) which could be a limiting factor in confirming the diagnosis. Thus, BAL BDG positivity without isolation of Candida in a respiratory specimen does not have much significance. We advocate the combined use of BAL BDG and isolation of Candida from respiratory samples (BAL/tracheal aspirate) for the diagnosis of Candida pneumonia particularly in conditions in which histopathological examination is not feasible. In addition, the aforementioned approach should be rewarding in cases with a high pretest probability of pulmonary candidiasis. Further prospective studies on a large scale are needed to validate this approach. The germ tube antigen, mannan antigen/antibody detection, and PCR methods have not been validated for the detection of Candida pneumonia. The only method to confirm the diagnosis is obtaining a lung biopsy and demonstration of yeast or hyphae along with inflammatory cells, which is sometimes not viable in critically ill patients.

In cases with biopsy-proven candidiasis, the decision is straightforward. Echinocandins are the drug of choice for invasive candidiasis. However, the poor clinical condition of the patients may preclude histological diagnosis in most cases. The initiation of therapy based on BAL positivity is not recommended due to the poor correlation of BAL findings with biopsy [22]. A study by Wood et al. [22] described the positive and negative predictive value of BAL culture, 29% and

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89%, respectively. Furthermore, in their report, only 2% of patients were given antifungal therapy, and none of the patients developed candidemia despite not receiving antifungal treatment. The mortality rate was also found similar in patients who did not receive antifungal therapy in comparison with those who received treatment based on isolation of BAL Candida [22].

reports describing the interaction of Candida species and various bacterial organisms (particularly Pseudomonas and Staphylococcus species) which are common in the setting of ICU (ventilator-associated pneumonia) [23–25]. The detection of Candida in the setting of ventilator-associated pneumonia (VAP) was reported as an independent predictor of increases in mortality and length of hospital stay [23, 25].

Candida albicans can also promote the mixed-species biofilm formation (along with S. aureus) which confers more antimicrobial resistance and persistence of pathogenic bacteria inside the respiratory tract [26].

DISCUSSION:

HISTORY AND EXAMINATION (TABLE 1):			
PARAMETERS	CASE 1	CASE 2	CASE 3
AGE / SEX	15/ M	30/M	69/M
DURATION OF SYMPTOMS	1 month	3 to 4 months	1 to 2 months
CO MORBIDITIES	Type 1 DM	No	COPD
ON ATT INTAKE BASED ON CLINICO-RADIOLOGICAL BASIS	Yes, On ATT for 1 month	Yes , on ATT for 2 months	No
OPHTHAL EXAMINATION	WNL	WNL	WNL
ORAL EXAMINATION	WNL	WNL	White patches were seen – swab negative
INVESTIGATIONS (TABLE 2):			
ANAMEIA	Yes (9.2)	Yes (9.0)	no
HIV	Negative	Negative	Negative
AREA OF LUNG INVOLVED	Bilateral lung (right middle and lower lobe and left lower lobe)	Bilateral diffuse involvement	Bilateral lung involved
DURATION OF EMPIRICAL ANTIBIOTICS	More than 2 weeks	More than 2 week	More than 1 week
DIAGNOSED BY	Endo bronchial	Endo bronchial	Endo bronchial

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	Biopsy (intra luminal growth seen)	Biopsy (mucosal irregularity)	Biopsy (mucosal irregularity)
ANTI FUNGAL THERAPY	T. Itraconazole	T. fluconazole	IV. fluconazole
FOLLOW UP			
1 week	Fever reduced; appetite improved	Fever reduced	Fever reduced Appetite improved
1 month	Cough decreased and sugars came into control, Weight improved	Cough and expectoration were reduced, Weight improved	Weight improved
PROGNOSIS	Good	Good	Good

Patients in ICU with long stay with no particular diagnosis should be subjected to invasive procedures like bronchoscopy based on risk benefit ratio. Such procedures can be lifesaving in many patients especially in young patients .

This case series deals about 3 patients with different age group presentation with varying duration of symptoms. 2 of 3 patients were started on tubercular drugs on clinical basis before presenting to us. All were retroviral negative and showed bilateral lung involvement. They were started on long term empirical antibiotics as their respiratory cultures (sputum, tracheal secretions) were negative, But patients weren't improving . Hence, they were subjected for bronchoscopy following which biopsy was taken from abnormal sites which showed pseudo hyphae with raised inflammatory cells. Following which they were started on antifungal theraphy which showed clinical improvement. They were followed up on 1week and after 1 month, they all showed good clinical improvement.

CONCLUSION: The decision to start antifungal treatment should be done on a tailored approach. Additionally, antifungal therapy may be initiated in immunodeficient patients ,those not improving with antibiotics and without an alternative etiology. We recommend all respiratory critical patients who are not improving on long term empirical antibiotics should be subjected to bronchoscopy guided tissue diagnosis for further management of the patient which is been neglected in day to day times .

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Conflicts of interest : There are no conflicts of interest.

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