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A Series of Six Cases of Candida Ciferrii Infection in a Tertiary Care Centre of North India

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Authors' contributions

This work was carried out in collaboration between all authors. Author SU did the compilation of cases, collected the clinical details of the patients and wrote the first draft of the manuscript. Author TW conceptualised the study, managed literature searches and edited the manuscript. Author SS managed the analysis of the study and also edited the manuscript. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Aim: We aim to understand the role of *Candida ciferrii* (*C. ciferrii*) as a pathogen for invasive mycosis.
Presentation of Cases: We report six cases of patients with invasive disease due to *C. ciferrii* from a tertiary care centre of North India in one year. Among the six cases, two cases are of candidemia, three from lower respiratory samples and one from drainage fluid.
Discussion: Fungal infections especially candidiasis may occur in immunocompromised patients or in patients with associated co-morbidities. Candidiasis increases both the morbidity and mortality. *C. ciferrii* has been rarely reported as cause of human infection. It may not be the primary pathogen but has the potential to exacerbate the existing pathology.
Conclusion: Rare and unusual pathogens should not be ignored. They should be reviewed in accordance with the patient's clinical manifestations and treated promptly to improve the prognosis of patient in appropriate clinical conditions.

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1. INTRODUCTION

In the fifth century B.C., Hippocrates described thrush (first described yeast infection) which was later confirmed by Berg and Gruby [1]. Since then, many forms of candidiasis have been demonstrated, some of which are life-threatening. With the advent of new modalities for treatment of cancer, increasing use of intravenous catheters and broad spectrum antimicrobial agents, rise in the number of patients with immunocompromised conditions has paved the way for innocuous yeasts to cause serious infections [2,3,4]. Invasive infections related to yeast are increasingly observed in immunocompromised patients in hospitals. [5,6] Fungal infections have increased morbidity & mortality and prolonged hospital stay which can lead to rise in medical care costs [7]. There are more than 20 species of *Candida* that have been shown to cause disease in humans. *C. albicans* is most frequently associated with human infections [2]. Non-albicans *Candida* species have been increasingly found as causative agents in human infections with important therapeutic implications [8]. The unusual yeast species *C. ciferrii*, was first described in 1965 [9], and it was named in honor of the memory of Prof. Dr. R. CIFERRI. It is the anamorph of *Stephanoascus ciferrii* and has been described as a pathogen in superficial mycoses and infrequently as a systemic disease [5].

2. PRESENTATION OF CASES

Case 1:

A 70 year old, hypertensive male patient, known case of Benign prostatic hypertrophy (BPH) and COPD (Chronic obstructive pulmonary disease), presented with complaints of shortness of breath and cough with expectoration since 2 months. The patient was hemodynamically stable. Pulse was 102/min, RR (Respiratory rate) - 26/min, BP (Blood pressure) - 140/80mmHg. On auscultation of chest - bilateral diffuse ronchi were present.

His initial laboratory investigations showed Hb (Hemoglobin) - 12.4gm/dl, Total leukocyte count (TLC) was 10.99/mm^3 with neutrophil 75.8%. His glycosylated Hb – 5.8% indicating pre-diabetic status. His CRP (C-reactive protein) was 54.7mg/l, ESR (Erythrocyte sedimentation rate) - 69 mm/hr and procalcitonin - 0.09 ng/ml. His RFT (Renal function test) & LFT (Liver function test) parameters were within normal limits.

Sputum was sent for Gram's stain, AFB (Acid fast bacilli) stain, KOH (Potassium hydroxide) mount and culture. Gram's stain showed many gram positive cocci in pairs & short chains suggestive of commensal flora, AFB stain and KOH mount were negative. Sputum culture did not grow any pathogenic organism.

BAL (Bronchoalveolar lavage) was sent for cytological examination, Gram's staining, fungal staining, AFB staining, malignant cells, mycobacterial culture, and fungal culture. Respiratory multiplex PCR was negative. On Gram's staining moderate number of pus cells, few gram positive cocci and moderate number of budding yeast cells (BYC) were seen. The fungal culture had growth of BYC which were processed for ID (Identification) and antifungal susceptibility testing (AFST) in VITEK 2 (bioMérieux, Marcy L'Etoile, France). The isolate was identified as *C. ciferrii* and was susceptible to all the antifungal agents.

His chest X-ray showed blunting of the left CP (costo-phrenic) angle. Biopsy of endobronchial growth showed squamous cell carcinoma (SCC). Medical oncology opinion was taken for SCC lung.

Patient was managed with IV (Intravenous) antibiotics, IV fluids, nebulisation and other supportive medications. He was given oral fluconazole (150mg) daily for 14 days. Patient tolerated first cycle of chemotherapy well without any major problems and was discharged in a stable condition and advised to follow up in OPD.

Case 2:

This is a case of 67 year old male, with a history of hypertension, diabetes mellitus, diabetic nephropathy, malnutrition and morbid obesity suffering from atherosclerotic heart disease. He has undergone coronary artery bypass surgery.

Patient was admitted under CTVS (Cardiothoracic & Vascular Surgery) with complaints of fever and shortness of breath. His initial laboratory investigations showed Hb - 11gm/dl, TLC - 19.96/mm^3 with neutrophil 91.1%. His RFT & LFT parameters were deranged. His procalcitonin was 8.62 ng/ml. Chest X-ray

showed atelectasis on left lower zone and cardiomegaly. Ultrasound whole abdomen showed grade III fatty liver, distended gall bladder and urinary bladder. NCCT (Non-contrast computerized tomography) abdomen visualised lung bases showing bilateral mild pleural effusion with adjacent collapse and consolidation in basal segments of both lower lobe.

Blood, urine and BAL samples were received in microbiology laboratory for Gram's staining, culture and respiratory multiplex PCR. Respiratory multiplex PCR was negative. Urine and BAL cultures were sterile. The blood sample showed growth of BYC which was identified as *C. ciferrii* by VITEK 2 automated identification system. The isolate was susceptible to all the antifungal agents. Patient also had a similar fungal infection in sacrum. He was started on oral fluconazole and sertaconazole ointment, but patient died.

Case 3

This is a case of 52 year old male patient, with history of left ventricular failure, bronchiectasis, tuberculosis and COPD. Patient was admitted under Respiratory and sleep medicine team with the complaints of hoarseness, cough and difficulty in breathing. His initial laboratory investigations showed Hb - 15.4gm/dl, TLC - 11.73/mm^3 with neutrophil 75.1%, CRP was 49.2mg/l. His RFT & LFT parameters were deranged. His procalcitonin was 0.05 ng/ml.

The X-ray report showed extensive fibrotic opacities seen in left lung and right upper zone with pulled up hilum and mediastinal shift towards left. Blunting of left CP angle was noted which is suggestive of pleural effusion.

Sputum sample was received for Gram's stain and fungal culture. Gram's stain showed BYC. Culture showed growth of yeast on SDA (Sabouraud Dextrose Agar). *C. ciferrii* was identified by VITEK 2. AFST showed MICs as, fluconazole (≥16µg/ml) and amphotericin B (2µg/ml) and echinocandins (≥4µg/ml). Patient was started on antibiotics, IV fluids and nutritional support. He was given caspofungin for 14 days. Patient responded to the given treatment. Patient was discharged in stable condition with advice and medication.

Case 4:

This is a case of 59 years old female patient, known case of carcinoma cervix, atherosclerotic heart disease, and neuralgia. She was on chemotherapy. Patient was admitted under Gasteroenterology team and relevant investigations were done. Her initial laboratory investigations showed Hb – 10.2gm/dl, TLC - 29.01/mm^3 with neutrophil 90%, CRP was 38mg/l, procalcitonin was 0.31. Her RFT & LFT parameters were deranged.

The ultrasound (USG) KUB (Kidney, ureters and bladder) showed right side moderate hydronephrosis and left side mild hydronephrosis seen. The radiograph of KUB shows DJ stent on right side of lower abdomen.

Drainage fluid was sent for Gram's stain and culture. The Gram's stain showed BYC and SDA culture growth was identified as *C. ciferrii*. The AFST revealed MICs to fluconazole (≥64µg/ml) and amphotericin B (4µg/ml) and susceptibility to echinocandins (<1µg/ml) and flucytosine (<1µg/ml). Patient was started on antibiotics, IV fluids and nutritional support. She was started on caspofungin for 14 days. Patient responded to the given treatment. She was discharged with follow up date for chemotherapy.

Case 5:

This is a case of 75 years old male patient, known case of diabetes mellitus type 2, hypertension, bronchial asthma, chronic kidney disease, oral hypoglycemic agent induced hypoglycemia, BPH and permanent atrial fibrillation. He presented in the emergency department with complaints of breathlessness on exertion (Grade III -IV), bilateral pedal oedema, uneasiness and frequent micturition. Patient has no history of chest pain. On Admission patient was hemodynamically stable. His clinical examination revealed bilateral basal crepts and bilateral pedal edema. Laboratory investigations revealed Hb 9.5, WBC 10.36/mm^3, neutrophil 91.9.

Blood and urine culture came out to be negative. The KOH mount of sputum showed BYC with pseudohyphae which was identified by VITEK 2 as *C. ciferrii*. The isolate was susceptible to fluconazole (≤1µg/ml), voriconazole (≤0.12µg/ml) and flucytosine (≤1µg/ml), while there were higher MICs for amphotericin B (4µg/ml), caspofungin (≥4µg/ml) and micafungin (≥4µg/ml). USG chest was suggestive of bilateral mild pleural effusion, right side volume measuring approximately 100-150cc and left side volume measuring approximately 50-100cc. Lung

ventilation/perfusion scan revealed scintigraphic findings consistent with probability for pulmonary embolism.

During hospital stay patient was managed with IV antibiotics, IV fluids, nutritional support and supportive measures. He was given oral fluconazole for 21 days. Patient responded well to the given treatment. Patient was discharged in stable condition.

Case 6:

A 36 years old male, a known case of RV (Right ventricular) mass with bilateral pulmonary thromboembolism and pericardial effusion was admitted in ICU with breathlessness and persistent fever. He had to be intubated and kept on ventilatory support.

Laboratory investigation revealed TLC – 28.33/mm^3, neutrophil – 88.6%, Hb – 10.5gm/dl. LFT and RFT were deranged. Blood and urine samples were sent for culture and susceptibility testing. Urine culture was negative. There was growth of BYC in blood culture that was identified as *C. ciferrii* by VITEK 2 system. The AFST showed higher MIC to fluconazole (16µg/ml), while for other antifungals it was susceptible, voriconazole (1µg/ml), micafungin (2µg/ml), amphotericin B (0.5µg/ml) and flucytosine (≤1µg/ml).

The patient, however, had sudden cardiac arrest and died.

3. DISCUSSION

Candida species is part of the normal flora of human skin, oropharynx, lower gastrointestinal tract, and genitourinary system [3,4,5,8,9]. The incidence of deep *Candida* infections resistant to common antifungal agents has increased in recent years especially among patients having immunocompromised conditions such as diabetes mellitus, malignancy, prolonged high dose glucocorticoid use, transplant recipients, and HIV patients [3,4,8]. *Candida* species are routinely isolated from respiratory specimen of patients, but accompanying lung parenchymal invasion is infrequent. The most common cause of COPD exacerbations has been found to be respiratory tract infections mainly of bacterial or viral origin. Fungal pneumonia which is infrequent may cause exacerbation especially in immunocompromised individuals. Demonstration of *Candida* species from lower respiratory tract along with parenchymal invasion is possible indicator of *Candida* pneumonia [3].

C. ciferrii is an unusual species of *Candida*, which has been rarely reported as a cause of human infection mostly in patients with immunosuppression [3,5,6,7,9]. Most of the reported *C. ciferrii* cases include malignant otitis externa and onychomycosis [2,10]. A fatal case of multi-drug resistant strain of *C. ciferrii* isolated from blood culture of a child was reported by Agin et al. [11] However, among the *C. ciferrii* isolates in our study, one case of candidemia was susceptible to all the antifungals while it was fluconazole resistant in case 2. In the literature, we found two cases of lung involvement by *C. ciferrii*, one in the form of spotted pulmonary infiltrations and the other as exacerbation of COPD, similar to 3 cases in our study [3,5]. The *C. ciferrii* strain in one case with acute exacerbation of COPD was resistant to fluconazole [5] and in two cases it was resistant to amphotericin [3]. Amongst the presented cases, two cases of lower respiratory tract infection (case 3 & 6), had higher MICs to echinocandins. The patient profile of the six cases and exacerbation of their conditions after infection with *C. ciferrii* suggest that we should not ignore the isolation of unusual *Candida* species. Since there is a lot of variability in antifungal susceptibility pattern of this fungi, we must perform the AFST before starting the antifungal therapy [3,7,10,11].

4. CONCLUSION

It is important to consider unusual pathogens as the probable cause of infection, especially in immunocompromised, previously treated, or patients with a prolonged hospital stay. With the increasing trend of resistance to antifungal agents among non-albicans *Candida* species, performing AFST has become a necessity to guide clinicians in treating fungal infections.

CONSENT AND ETHICAL APPROVAL

As per university standard guideline participant consent and ethical approval has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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