DOI: 10.7860/JCDR/2023/67157.18759

Case Report

Microbiology Section

Invasive Aspergillosis and Candidiasis in a Patient with Supraglottic Carcinoma undergoing Chemoradiotherapy: A Case Report

NEETHU BABU[1], CHITRALEKHA SAIKUMAR[2], JOMON RAPHAEL CHALISSERY[3]

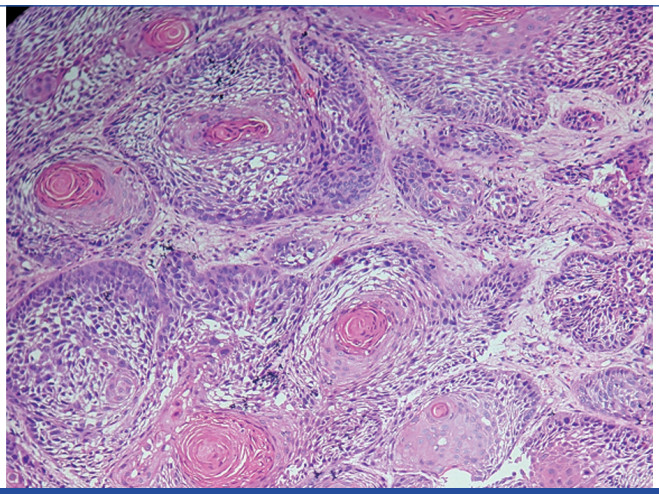
ABSTRACT

The incidence of Invasive Aspergillosis (IA) is increasing. Early diagnosis and treatment are very important to improve patient survival, especially in immunocompromised patients. The diagnosis of IA is challenging as clinical indicators are limited, and early microbiological confirmation of the infection is infrequent. Here, the authors present the case of a 43-year-old male who was undergoing radiotherapy along with concurrent chemotherapy for carcinoma supraglottis. He developed Invasive Pulmonary Aspergillosis (IPA) along with candidiasis within two weeks of therapy. Voriconazole remains the recommended therapy for patients with IA, which also acts against fluconazole-resistant *Candida* species.

Keywords: *Candida*, Radiotherapy, Voriconazole

CASE REPORT

A 43-year-old, male patient, was referred to the Radiation Oncology department with a persistent sensation of a foreign object in the right-side of his throat and painful swallowing for a period of six months. Additionally, he reported a change in his voice for the last month, along with experiencing earache on the right-side. No co-morbidities or risk factors were noted. On examination, no palpable neck or supraclavicular nodes were present. A 90-degree rigidscopy showed a well-defined soft tissue lesion (25×11.5×21.3 mm) in the right lateral hypopharynx protruding into the lumen, likely from the pyriform fossa, suggestive of neoplastic aetiology. A punch biopsy from the supraglottic growth showed well-differentiated squamous cell carcinoma [Table/Fig-1]. He was diagnosed with Carcinoma supraglottis, stage T2N2bM0. Radical radiotherapy was planned with concurrent chemotherapy weekly using injection cisplatin. He received radiation treatment using Intensity Modulated Radiation Therapy (IMRT) technique in the head and neck region. The dose and fractionation were 70Gy/35 fractions with concurrent chemotherapy with injection cisplatin 40 mg/m^2.

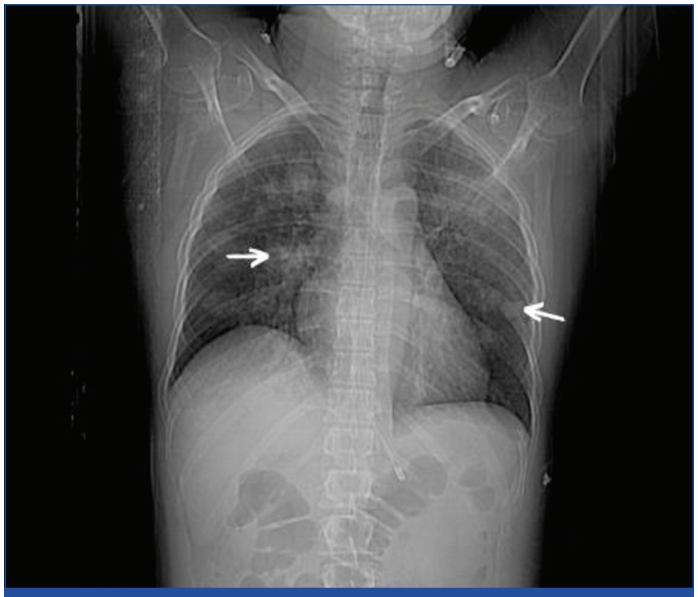


[Table/Fig-1]: Punch biopsy from supraglottic growth showing squamous cell carcinoma (H&E, 40X).

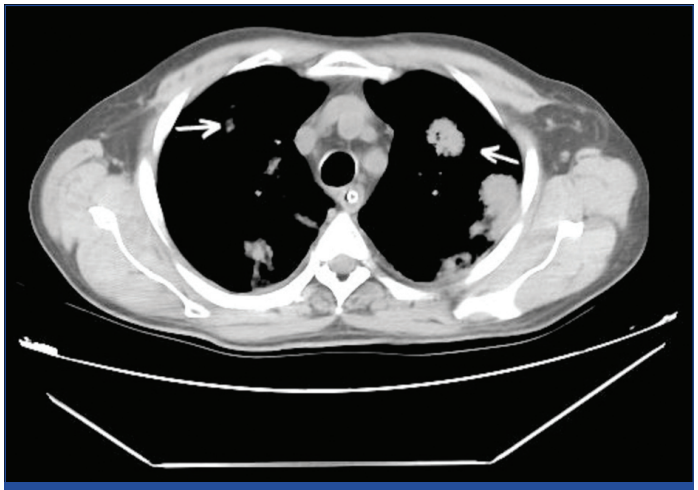
After two weeks of radiation therapy and two cycles of concurrent chemotherapy, he developed a sudden onset of fever, generalised tiredness, dyspnoea, and loose stools. He was admitted to the hospital, and routine blood investigations were performed, revealing severe neutropenia. The laboratory data were as follows: white cell count 0.11×10^3/µL with 18.2% neutrophils and 81.8% lymphocytes, haemoglobin 8.7 g/dL, haematocrit 24.5%, and platelets 50,000/µL [Table/Fig-2]. Tests for dengue serology, H1N1, and malarial parasites were negative. He was managed conservatively with intravenous growth factors, fluids, and was started on antibiotic Piperacillin-Tazobactam 4.5 g intravenous every eight hours and fluconazole 150 mg once daily. Stool and blood cultures were sent, and he was shifted to the ICU for better care. The culture reports were negative, but his fever persisted. The antibiotic was changed to Injection Meropenem 1.5 g twice daily, and Tab Voriconazole 200 mg once daily was started. A chest X-ray was taken, which showed patches in the lung [Table/Fig-3]. A High-Resolution Contrast Tomographic (HRCT) scan of the chest revealed signs of IA [Table/Fig-4]. Bronchoscopy was performed, and Bronchoalveolar Lavage (BAL) was sent for culture, and a Galactomannan (GM) test was also done. The GM test [1] by lateral flow assay showed a value of 10.22, which was positive (an index value of ≥0.50 is positive and <0.5 is negative). His BAL and sputum culture showed *Candida* species growth [Table/Fig-5]. VITEK identification and sensitivity testing were performed, which identified the species as *Candida glabrata*, which was resistant to fluconazole. The strain was sensitive to Voriconazole with a very low minimum inhibitory concentration value (0.12). Voriconazole 200 mg twice daily was continued, and the patient improved. His serum GM was checked after seven days, and it was 1.32. The laboratory data were as follows: white cell count 24.4×10^3/µL with 87.5% neutrophils and 4% lymphocytes, haemoglobin 8.5 g/dL, haematocrit 25.1%, and platelets 100,000/µL [Table/Fig-2]. He was shifted from the ICU on the 18th day and was advised best supportive care.

Blood test parameter	At the time of infection	During treatment
White blood cell count (/µL)	0.11×10^3	24.4×10^3
Neutrophils (%)	18.2	87.5
Lymphocytes (%)	81.8	4
Haemoglobin (g/dL)	8.7	8.5
Haematocrit (%)	24.5	25.1
Platelets (/µL)	50,000	100,000

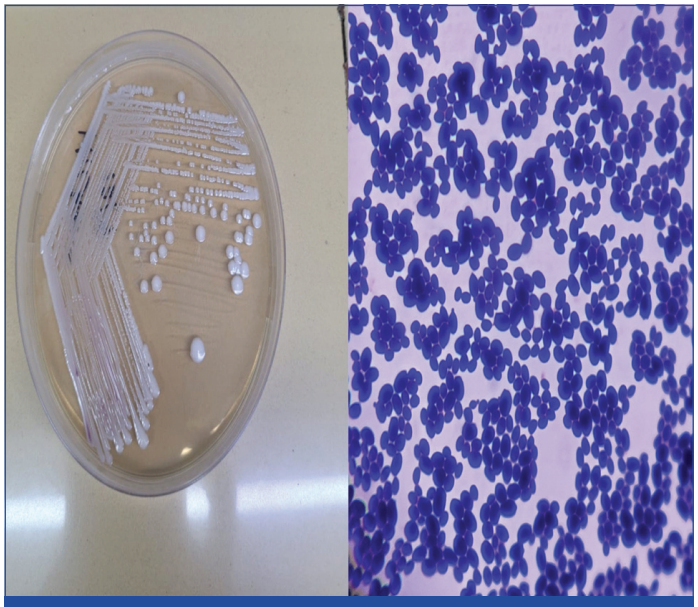
[Table/Fig-2]: Haemogram at the time of infection and during treatment.



[Table/Fig-3]: Chest X-ray showing patches in both lung lobes.



[Table/Fig-4]: High-Resolution Contrast Tomographic (HRCT) scan of chest showing multiple patchy round or round-like opacities.



[Table/Fig-5]: *Candida glabrata* growth on Hichrome agar plate and Gram stained smear showing gram positive budding yeast cells, at 100x.

DISCUSSION

The frequency of IA infections is increasing due to multiple factors. This rise in occurrences can be linked to a notable surge in patients receiving immunosuppressive therapy, along with their enhanced recovery rates from once-deadly bacterial infections [2]. Patients with solid tumours are believed to have a low risk for IA, as per the study by Pagano L et al., [3]. The patient presented in this report, who was receiving cisplatin chemotherapy along with radiation, was at a low-risk of developing IPA. He received standard doses of fluconazole against *Candida*, which is recommended for patients with neutropenia who are on chemoradiotherapy. Even with fluconazole prophylaxis, the patient developed candidiasis along with IA. The *Candida* species isolated was *C. glabrata*, which shows acquired resistance to fluconazole. Previously, mixed fungal infections have been documented; however, *Candida albicans*, the recognised pathogenic species, was the predominant occurrence [4].

To achieve favourable clinical outcomes in these patients, it is crucial to begin effective systemic antifungal treatment promptly. However, diagnosing IA can be challenging, as clinical indicators are limited, and early microbiological confirmation of the infection is infrequent. Obtaining a definitive diagnosis of the condition requires a tissue biopsy that allows direct visualisation of the branching septate hyphae through microscopic examination or recovery of the organism itself. However, obtaining tissue samples can be challenging in patients with thrombocytopenia or coagulation disorders, and it may not be feasible in individuals with high oxygen requirements [5].

Due to the challenges in obtaining tissue samples and the varying success rates of traditional cultures, clinical diagnosis relies on pulmonary Computed Tomography (CT) scan results and non culture-based diagnostic methods, such as detecting GM or DNA in blood or BAL samples [6,7]. These techniques help healthcare providers identify and manage invasive *Aspergillus* infections early, leading to better treatment outcomes for this vulnerable patient population. One widely used approach involves detecting the presence of GM. GM is a type of polysaccharide found in the cell wall of *Aspergillus* fungi, and it is released when the fungus grows. However, the sensitivity of this testing method can vary and depends on the immune status of the host. It tends to have higher sensitivity in patients with haematologic malignancies compared to those with milder levels of immune suppression [8]. Patients on antifungal therapy may experience falsely negative GM results. Historically, false-positive GM results have been observed in patients receiving certain antibiotics like piperacillin-tazobactam and amoxicillin-clavulanate. However, recent reports suggest no cross-reactions with piperacillin-tazobactam [9,10]. Of particular interest is the ability to detect GM in lavage samples that show no growth in cultures [11]. In the present case, although the BAL sample was sent for culture, it only grew *Candida.*

Candida albicans was the most commonly isolated species from head and neck cancer patients undergoing chemoradiotherapy, but recently non-albicans *Candida* species, especially *C. tropicalis* and *C. glabrata*, have been increasingly reported in these patients [12]. The increased incidence of invasive candidiasis with *C. glabrata* is linked to the extended use of broad-spectrum antibiotics and corticosteroids, intensive chemotherapy, and prior fluconazole prophylaxis for antifungal protection. *C. glabrata* strains exhibit acquired resistance to fluconazole [13,14].

Patients at high-risk for aspergillosis who receive preemptive antifungal treatment, supported by laboratory and imaging results, can expect the most favourable outcomes. Voriconazole is considered the best systemic antifungal treatment, as it has demonstrated significant superiority over conventional amphotericin B. Consequently, it has notably improved survival rates in patients with this condition [15]. The patient presented in the current report also responded well to voriconazole. Voriconazole has also shown a more favourable side-effect profile and better overall tolerability. When initial therapy is ineffective or not well tolerated, echinocandins like caspofungin are used as salvage therapy [7]. Given the differing mechanisms of action of azoles, trienes, and echinocandins, combining these therapies could be a potential strategy for treating IPA [7]. However, currently, voriconazole is considered the treatment of choice for IPA [7,15].

CONCLUSION(S)

The challenges associated with acquiring tissue samples and the inconsistent effectiveness of conventional microbiological cultures have prompted a shift towards alternative diagnostic approaches for invasive *Aspergillus* infections. The reliance on pulmonary CT scans and advanced non culture methods, such as the detection of GM in blood or BAL samples, has become pivotal in the clinical diagnosis of these infections. These techniques enable early identification and management of IA, leading to improved treatment outcomes. Voriconazole remains the recommended therapy for patients with IA. The reported case and broader evidence highlight the efficacy of voriconazole and its favourable side-effect profile, enhancing its overall tolerability.

Acknowledgement

Authors are grateful to the Department of Radiodiagnosis and to Dr. Geetha CG, Assistant Professor, Department of Pathology, Amala Institute of Medical Sciences, Thrissur, Kerala, India for the images.

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PARTICULARS OF CONTRIBUTORS:
1. Research Scholar, Bharath Institute of Higher Education and Research, Chennai, Tamil Nadu, India; Tutor, Department of Microbiology, Amala Institute of Medical Sciences, Thrissur, Kerala, India.
2. Professor and Head, Department of Microbiology, Sree Balaji Medical College and Hospital, Chennai, Tamil Nadu, India.
3. Professor and Head, Department of Radiation Oncology, Amala Institute of Medical Sciences, Thrissur, Kerala, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Jomon Raphael Chalissery,
Professor and Head, Department of Radiation Oncology, Amala Institute of Medical Sciences, Thrissur-680555, Kerala, India.
E-mail: joeraphael@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Aug 25, 2023
- Manual Googling: Oct 02, 2023
- iThenticate Software: Oct 16, 2023 (3%)

ETYMOLOGY: Author Origin

EMENDATIONS: 6

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Aug 22, 2023**
Date of Peer Review: **Sep 18, 2023**
Date of Acceptance: **Oct 18, 2023**
Date of Publishing: **Dec 01, 2023**