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CASE REPORT

Cryptococcosis in oncology patients: a case series in a tertiary care cancer centre

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ABSTRACT

Cryptococcosis, a relatively uncommon infection in cancer patients is often associated with delayed diagnosis and high fatality rate due to its highly heterogeneous and protean manifestations. Early recognition and initiation of appropriate antifungal therapy might have a favourable outcome in such cases. Here we report three cases of Cryptococcosis among cancer patients in a tertiary care cancer centre in South India.

All three patients were males of different ages at presentation with immunosuppression in the form of solid organ or hematologic malignancy and were using immunosuppressive medications like steroids or chemotherapeutic agents. They presented with cryptococcemia and cryptococcal meningitis. Patients with microbiologically proven cryptococcosis had poor outcome in this subgroup of patients.

Keywords: Cryptococcosis; Immunosuppression; Hodgkin lymphoma; Adenocarcinoma; B cell lymphoma; Opportunistic pathogen

INTRODUCTION

Invasive fungal infections are on the rise in immunocompromised patients. Cryptococcosis is a common fungal infection in HIV patients, but relatively uncommon in oncology patients and its association with cancer has not been well studied. In immunosuppressed individuals, it can present as disseminated infections, meningitis, pulmonary infections, pericarditis, cutaneous and various other extrapulmonary and neurological manifestations (1-7). Manifestations of cryptococcosis in cancer patients are varied leading to diagnostic dilemmas and delay in initiation of appropriate treatment. Cryptococcus infection when not associated with HIV has very few evidence based recommendations for treatment (8, 9). Here we report three cases of systemic cryptococcosis with encapsulated yeast, *Cryptococcus neoformans* among cancer patients to understand its clinico-mycological profile.

CASE PRESENTATION

The following case series is that of three patients attending Regional Cancer Centre in South India who developed cryptococcosis in September 2015, February and April 2021 respectively. They developed cryptococcosis during induction phase, maintainence phase and work up phase respectively.

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Case 1. A 66-year-old man, a driver by profession, a known case of prostate adenocarcinoma with extensive liver, nodal and skeletal metastasis and a pre-existing diabetes and hypertension on medication who was started on docetaxel-based chemotherapy with zoledronic acid and steroids. He developed fever and backache of 2 days duration in February 2021. X-ray Kidney, ureter and bladder (KUB) showed a doubtful perinephric collection for which an ultrasonography was planned. But ultrasound was deferred because he developed sepsis with high-grade fever. His routine haematological investigations have been summarised in Table 1. Two blood samples from different venepuncture sites was taken in automated BACT/ALERT®blood culture bottles (bioMérieux) before starting him on broad-spectrum antibiotics and sent to Microbiology Division. Urine culture was also done.

In our lab, we received a pair of automated BACT/ALERT®blood culture bottles (bioMérieux) which were loaded into the BACT/ALERT 3D instrument without further delay. After 85 hours of incubation, both the bottles flagged positive. Microscopy of the flagged blood culture bottle showed budding yeast cells with the suggestion of capsule which was confirmed by negative staining with India ink. After 48 hours of incubation, mucoid creamy non-pigmented non-haemolytic colonies grown on blood agar and chocolate agar. Creamy white colonies were observed on Sabouraud Dextrose agar. The isolate was rapid urease positive. It also assimilated glucose and did not ferment any sugars. This isolate was tentatively identified as *Cryptococcus neoformans* based on microscopic examination, the presence of capsule with negative ink staining, a positive latex agglutination test, a rapid urease test, and biochemical reactions, and was later confirmed by VITEK 2. As both the Clinical and Laboratory Standards Institute (CLSI) and the European Committee for Antimicrobial Susceptibility Testing (EUCAST) do not have any clinical breakpoints for *C. neoformans* for fluconazole and other antifungal agents, the epidemiological cut offs (ECV) of fluconazole, amphotericin B, 5-flucytosine as per the study conducted by Espinel-Ingroff et al. were taken for the study (10). Microbroth dilution was used to assess the minimum inhibitory concentration (MIC) for the antifungal drugs fluconazole and amphotericin B. MIC of flucytosine was assessed by VITEK 2. The strain was found to be sensitive to these drugs. Following the development of sepsis, he was admitted to a tertiary care centre and started on carbapenems. After the issue of preliminary report, carbapenems was stopped and he was started on liposomal Amphotericin B. Despite antifungal medication and good supportive care, the patient died after 15 days of treatment.

Case 2. 37-year-old man, a housekeeping staff at a resort and a known case of hypothyroidism in alternative medicine recently diagnosed with T cell-rich B-cell lymphoma stage 4 with bone marrow and CSF involvement (predominantly CD 4^{+}), was admitted

Table 1. Haematological investigations of the patients

S. No	Blood Investigations	Case 1	Case 2	Case 3
1	Haemoglobin	11.4 gm/dl	12.4 gm/dl	14.3gm/dl
2	Total count	6200 cells/mm^3 with neutrophil predominance 93%	3500 cells/mm^3 with neutrophil predominance 61%	15600 cells/mm^3 with neutrophil predominance 73%
3	Random Blood Sugar	206mg/dl	136mg/dl	108mg/dl
4	Blood urea	21 mg/dl	27 mg/dl	22 mg/dl
5	Serum creatinine	0.8 mg/dl	0.7 mg/dl	0.7mg/dl
6	Serum sodium	127 meq/l	136 meq/l	136meq/l
7	Serum potassium	3.7 meq/L	5.6 meq/L	3.6meq/l
8	Serum bilirubin	-	0.8 mg/dl	0.9mg/dl
9	SGOT/SGPT	-	56/53	58/130
10	Serum alkaline phosphatase	-	248 U/L	131 U/L
11	Serum total protein	-	6.6 g/dl	6.7mg/dl
12	Serum albumin/globulin	-	4.2/2.5	3.6/3.1
13	LDH	-	202 u/L	-
14	Serum procalcitonin	-	-	1.78

for completion of workup and supportive care in April 2021. He also needed evaluation for persistent headaches. He presented with headache and vomiting of 2 weeks duration and recent onset of unsteadiness of gait. Viral markers were repeatedly negative. His routine haematological investigations have been summarised in Table 1. Blood cultures were negative. MRI brain showed a 5.2 mm nodular lesion in the right temporal lobe without significant oedema. CSF was sent for cytological, biochemical and microbiological studies. CSF protein was 46 mg/dl and CSF sugar was 38 mg/dl. CSF cytology was suggestive of lymphoma infiltration. CSF was also sent for culture. On inspection, CSF was turbid. Microscopy revealed many budding yeast cells with the suggestion of capsule which was confirmed by negative staining by India ink. Latex agglutination of the CSF sample was positive for cryptococcal antigen and the report was informed to the clinicians. A portion of the CSF sample was introduced into BACT/ALERT®blood culture bottles (bioMérieux) after taking sterile aseptic precautions and then loaded into the BACT/ALERT 3D instrument. After 72 hours of incubation, creamy white colonies were grown on blood agar and Sabouraud Dextrose Agar. The isolate tested positive for rapid urease. It also assimilated glucose and did not ferment any sugars. This isolate was tentatively identified as *Cryptococcus neoformans* and then confirmed by VITEK 2. Microbroth dilution was used to assess the minimum inhibitory concentration (MIC) for fluconazole and amphotericin B. MIC of flucytosine was assessed by VITEK 2. The strain had low MIC for amphotericin B, flucytosine and fluconazole.

The patient was started on liposomal amphotericin B which was given for one week, then - flucytosine 500 mg every six hours along with fluconazole 400 mg every twelve hours was added to the regimen due to persistent headaches. He was also put on intermittent CSF drain to relieve his symptoms. CSF cultures remained negative after the first positive culture but capsulated budding yeast cells could be demonstrated up to 10 weeks post initiation of therapy. However, he continued to get symptomatically better. During his treatment, he developed severe watery diarrhoea along with tiredness. His stool sample was sent for microscopy and culture. Formol ether concentration technique for ova and cysts of parasites revealed the presence of *Isospora* oocysts in the stool. During this episode, he developed severe hyponatremia and hypokalaemia with serum sodium to the amount 124 mg/dl, serum potassium 3.1 mg/dl and serum calcium 7.7 mg/dl. However, his diarrhoea improved with conservative and symptomatic management and trimethoprim-sulphamethoxazole was not prescribed.

Before the consolidation treatment was completed, he developed COVID-19 and had to be transferred to a COVID-19 care hospital after which he was lost to follow up.

Case 3. A 19-year-old man, diagnosed with classical Hodgkin's lymphoma and on MACOP-B regimen developed fever with increasing breathlessness after 3 months of initiation of chemotherapy in September 2015. His vitals were stable at presentation but there was a decreased air entry on the left side. CT scan of the thorax revealed a multifocal consolidation in the left upper lobe. Sputum culture was negative. His routine blood investigations have been summarised in Table 1. Lung biopsy was not sent due to of his poor general condition, while blood and CSF cultures were sent. His blood cultures yielded *Cryptococcus neoformans* on three separate occasions. The strain also had low MIC to the tested antifungal agents, namely -amphotericin B, flucytosine and fluconazole. CSF cultures were negative. He was started on parenteral amphotericin B after the issue of culture report. Unfortunately, the patient did not improve and worsened and died five weeks later.

The clinico-demographic profile of the three patients is compared and summarised in Table 2.

DISCUSSION

Cryptococcus neoformans is an opportunistic pathogen in people living with HIV. Patients with cancer are also prone to infection with *Cryptococcus neoformans*, but this association has not been well studied (11-14). Disseminated cryptococcosis is a life-threatening disease and is invariably fatal without treatment (12). Liposomal amphotericin B and flucytosine combination is the modality of treatment prescribed. But in countries like India, it is difficult to procure flucytosine and treatment is usually started with a single antifungal agent (13, 14). Cryptococcosis is a relatively uncommon fungal infection in cancer patients. During the past ten years, only three cases of cryptococcosis have been documented in our centre. Cryptococcosis in oncology patients has varying presentations like pulmonary nodules,

meningitis, bloodstream infections, or subcutaneous mass (1-7, 15, 16). Cryptococcosis can also develop at varying stages of the malignancy. The first patient was diagnosed with cancer six years before the first presentation. The second patient presented with coexisting *Cryptococcus neoformans* meningitis and lymphoma during his workup for the same and the third patient was on induction chemotherapy for Hodgkin lymphoma when he developed disseminated cryptococcosis. Studies from literature also suggest similar cases in patients with Hodgkin lymphoma (7, 15, 16). Our patients except for the second case had drug associated immunosuppression and were on high levels of steroids which made them susceptible to infection. All of them were male patients (17) and two of them recently diagnosed with haematological malignancy. The first patient had solid organ tumour (prostate adenocarcinoma). Two out of three patients had fever at presentation and both of them had positive blood cultures suggesting the presence of fever with cryptococcemia as a poor prognostic factor. Only the second patient showed a clinical response. However, he developed coexisting infection with *Isospora* species and SARS-CoV-2. Diagnosis of cryptococcosis was aided in our centre by microscopy, antigen detection and fungal culture. Combination therapy with liposomal amphotericin B and flucytosine seemed to improve the outcome in our patients. Two patients who received liposomal amphotericin B monotherapy died despite treatment.

In summary, our patients were immunocompromised due to their oncological conditions and had various manifestation of cryptococcosis. Two of them did not respond to treatment, indicating poor clinical outcome in this group of patients.

Table 2. Clinicodemographic data of the patients

Patient	Age	Sex	Malignancy	Comorbidity	Medication	Site	Pathology Correlation	Treatment	Co-infection	Course
1	66	M	Adenocarcinoma Prostate	Diabetes mellitus, hypertension	Docetaxel Zoledronic acid steroids	Blood	NA	Liposomal Amphotericin B	-	Died
2	37	M	T cell-rich B cell lymphoma stage 4 with bone CSF involvement	Hypo-thyroidism	Steroids	CSF	Present	Liposomal Amphotericin B for 1 week Liposomal Amphotericin B + Flucytosine 500 mg 6th hourly + injectable Fluconazole 400 mg 12 hourly from 2nd-week Parenteral Amphotericin B	Isospora diarrhoea after 1 month, after 3 months SARS-CoV-2	Lost to follow up
3	19	M	Classical Hodgkin's lymphoma	-	MACOP-B regimen	Blood	NA		-	Died

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