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## A FATAL CASE OF SINONASAL INVASIVE PENICILLIOSIS WITH DIFFUSE LARGE B-CELL LYMPHOMA


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A B S T R A C T

We report a case of Sinonasal Penicillium species with multiorgan dysfunction syndrome in a 64 year old female synchronously diagnosed with Diffuse Large B-Cell Lymphoma(DLBCL) having Diabetes Mellitus(DM) and Hypertension(HTN) admitted in our tertiary care hospital as a COVID 19 Suspect. Sinonasal Penicillium invasion is a rare, opportunistic, potentially fatal and acute invasive infection mostly affecting people with hematological malignancies. In this patient underlying DLBCL and Diabetes Mellitus could be the likely cause for Penicillium infection suggesting the need for vigilance in hospitalized patients with prompt diagnosis and timely management.



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The Editor

Subject : Submission of Manuscript for publication

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# A FATAL CASE OF SINONASAL INVASIVE PENICILLIOSIS WITH

# DIFFUSE LARGE B-CELL LYMPHOMA

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## ABSTRACT

We report a case of Sinonasal Penicillium species with multiorgan dysfunction syndrome in a 64 year old female synchronously diagnosed with Diffuse Large B-Cell Lymphoma(DLBCL) having Diabetes Mellitus(DM) and Hypertension(HTN) admitted in our tertiary care hospital as a COVID 19 Suspect. Sinonasal Penicillium invasion is a rare, opportunistic, potentially fatal and acute invasive infection mostly affecting people with hematological malignancies. In this patient underlying DLBCL and Diabetes Mellitus could be the likely cause for Penicillium infection suggesting the need for vigilance in hospitalized patients with prompt diagnosis and timely management.

## KEYWORDS

Penicillium, DLBCL, DM, COVID 19, Amphotericin B.

## INTRODUCTION

Penicillium species, inspite of being the most common fungi in the environmental surroundings, are often considered as non-pathogenic to human beings.1 However they can be a virulent pathogen and may cause death in immunocompromised host.2 Lungs, skin, nasal sinuses and brain constitute the major site of penicillium infection. A dysfunctional immune response along with an impaired mucosal barrier may predispose to penicilliosis. Use of corticosteroids along with these co existing risk factors is also a common cause for the disease. 3,4 Other predisposing conditions may include prolonged neutropenia, diabetes mellitus, haematological malignancy, hematopoietic stem cell transplantation or trauma. Immunocompromised state along with long term use of deferoxamine, long-term voriconazole prophylaxis or undergoing solid organ transplantation, or with iron overload also constitutes a major cause for penicillium infection.5,6

Penicillium spp. although considered as non pathogenic, are occasional causes of infection in human beings and the resulting infection is known as penicilliosis. Penicillium species has been commonly isolated from patients with otomycosis, keratitis, urinary tract infections, endophthalmitis, pneumonia, endocarditis, necrotizing esophagitis, peritonitis.

To add to its infectious potential, Penicillium verrucosumalso produces a mycotoxin known as ochratoxin A, which is carcinogenic and nephrotoxic.7 Penicillium marneffei infection known aspenicilliosismarneffei, is commonly acquired via inhalational route in immunocompromised hostscausing pulmonary infection later complicated by fungemia and disseminated infection.Later on usually involves the bones, liver, spleen and lymphatic system. Acne-like skin papules and lesions are observed during the course of illness on face, extremities and trunk.Penicilliosismarneffei infection along with immunocompromised or other risk factors is often a fatal disease.8,9

## CASE REPORT

We report a case of a 64 year old female from rural southern Maharashtra, a known case of hypertension and diabetes mellitus who was admitted as a suspected case of COVID 19 which came RTPCR negative, however was later diagnosed as Non Hodgkin Lymphoma – DLBCL, along with penicilliosis and multi organ dysfunction syndrome during the course of her hospital stay.

In September 2021 she presented to our tertiary care hospital with complaints of generalized weakness since past 1 month, dry cough since past couple of weeks and abdominal pain since few days. She also had history of intermittent moderate grade fever since a week for which she was admitted as a COVID 19 suspect considering the COVID pandemic and her RTPCR was sent. She had taken both doses of COVID vaccination. On admission she was afebrile, her pulse was regular 80 per minute and blood pressure was controlled on oral medications. Her random blood sugar was 220 mg/dl and had blood oxygen saturation levels of 92% on room air. She was started on oxygen by nasal prongs at 23 lit/minute, intravenous fluids, empirically on inj. ceftriaxone 1gm q12h, inj. pantoprazole, insulin, inj. paracetamol and other supportive care.

On admission her investigations were: -

She was transfused with 1 unit of whole blood. Her peripheral smear was unremarkable and dengue profile/Weil Felix test/ Widal tests were negative. Urine routine tests were within normal limits. Chest x-ray was suggestive of bilateral lower zone heterogenous opacities with perihilar shadows as shown in figure A. Her sputum and blood cultures were obtained before initiation of antibiotics. Later her culture reports didn't show any microbial growth and thereby she was continued on the same line of management.

On day 5 of admission, she started complaining of increasing severity of abdominal pain associated with per rectal bleed. Her USG abdomen was suggestive of moderate hepatosplenomegaly and multiple enlarged lymph nodes. Her blood counts were repeated which showed hemoglobin of 4.7g/dl, TLC 4860 cells/mm3 and platelet count 25000. In view of ongoing per rectal bleed she was transfused with 4 units of random donor platelet and was given a total of 3 units of whole blood transfusion during her course of hospital stay. Her CECT Abdomen and Pelvis was suggestive of hepatosplenomegaly with abdominal lymphadenopathy with renal deposits.

FIGURE 3 CT ABDOMEN

FIGURE 4 CT CHEST

Further her Bone Marrow Aspirate and Biopsy was done and reports were awaited. She was started on injection piperacillin + tazobactam and injection Levofloxacin and other supportive care. Over the next 2-3 days she was gradually tapered off O2 and was maintaining blood oxygen saturation levels around 96% on room air. Further on day 10 of admission she started complaining of difficulty in breathing with nasal congestion associated with headache and facial pain. MRI Orbit/Brain/PNS was done which showed heterogeneously enhancing soft tissue in bilateral frontal, ethmoidal and sphenoid sinus and was asked to rule out mucormycosis. Further nasal endoscopy was done along with sinus mucosal biopsy. The sample was sent for KOH mounts and culture sensitivity tests.

FIGURE 5 CT BRAIN

KOH mount reports were negative for fungal growth. She was empirically started on injection Amphotericin B Deoxycholate. Sinus mucosal samples were also sent for microscopy and culture sensitivity tests. Bone marrow aspirate and biopsy was sent for routine examination and immunohistochemistry.

Unfortunately patient started deteriorating haemodynamically and repeat blood reports showed haemoglobin 5g/dl, platelet count 29000/mm3, TLC 9000/mm3, serum creatinine 2.6mg%, blood urea levels 152 mg%, total bilirubin 6.8 (direct -3.4), SGOT-267, SGPT-118, ALP-510. She was then shifted to intensive care unit in view of hypotension and started on inotropic supports. Inj. Amphotericin B was withheld due to acute kidney injury and decreasing eGFR and MODS. Hemodialysis could not be done due to persistent hypotension inspite of inotropic support and finally she succumbed to death.

Later, her bone marrow reports were - MCV 78.2fL, MCH 25.7pg, MCHC 32.8 g/dL, WBC 5800/ul, platelet count 164000/ul.Atypical cells / Blasts 31 %, Neutrophils 19 %, Promyelocytes 02%, Monocytes 04 %, Myelocytes 08 %, Eosinophils 02 %, Metamyelocytes

06 %, Lymphocytes 20 %, Band forms 08 %, Erythroid precursors 20 % . IHC showed CD20, CD79a, BCL-2, MUM I Positive with Ki67 proliferative index of 50-60%; Features consistent with bone marrow involvement by Diffuse Large B-cell Lymphoma- NonGerminalcentre type.

Sphenoid Sinus Mucosal biopsy – culture and microscopy reports further showed penicillium spp. growth.

Figure 6 :- Greenish Mycelial colonies of Penicillium species on SDA media.

Figure 7 :- Paintbrush like appearance of Penicillium species along with chains of conidia.

DISCUSSION

Pulmonary infections with fungi, including *Penicillium* species, are associated with much higher mortality rates in patients with nosocomial infections or infections complicating organ failure .10*Penicillium* species can cause opportunistic infections.11Some patients with infections caused by *Penicillium* species have died despite treatment with ketoconazole , amphotericin B, or itraconazole.12

Penicillium-like fungi are commonly recovered from clinical samples, in routine hospital air surveys and in clinical practice, and are often encountered as airborne contaminants of culture specimens.13,14Often Penicillium species isolated from samples of non-AIDS patients are discarded as environmental contaminants and considered nonpathogenic. However, in immunosuppressed patients, non-marneffei species are being increasingly recognized as emerging opportunistic pathogens causing invasive fungal infections worldwide, with most reports involving P.citrinum, P.digitatum, and P.chrysogenum(Table 1)15-26.

TABLE 2:- Showing cases of penicillium species infection in haematological malignancies in various studies conducted.

BMT, bone marrow transplant; ALL, acute lymphoblastic leukemia; AML, acute Myeloid leukemia; MM, multiple myeloma; IFI, invasive fungal infection; BAL, bronchoalveolar lavage; AMB, amphotericin B deoxycholate; FCZ, fluconazole; PCZ, posaconazole; CSP, caspofungin; VCZ, voriconazole; ITZ, itraconazole; 5-FC, 5-flucytosine; MCZ, miconazole; DLBCL,Diffuse Large B Cell Lymphoma; NA, not available.

To summarise, as per the review, P.chrysogenum is considered to be the most prevalent species causing infection in immunosuppressed patients causing systemic and disseminated disease with invasive pulmonary infection. Conventional phenotypic methods may be not enough and difficult to confirm a diagnosis of Penicilliosis.Identification at the species level yet is challenging.27

With the Standard treatment for non-marneffei speciesnot yet been established and antifungal susceptibility data for clinically available antifungal agents and treatment options for infections caused by Penicillium species also being poorly understood, only data from T.marneffei has been published. In a recent study of 118 clinical isolates, (mainly from the respiratory tract/human bronchoalveolar lavage) terbinafine (TRB) and the echinocandins showed the best in vitro activity against Penicillium species with MIC<0.03lg/mL for TRB, azoles revealed variable activity with MIC ranges of 0.5lg/mL for posaconazole and 2lg/mL for voriconazole and itraconazole, 0.06lg/mL for caspofungin and anidulafungin, and 0.125 for micafungin; amphotericin B showed intermediate activity with MIC of 2lg/mL.28In conclusion, of importance, if normally sterile sites are involved in sampling, Penicillium spp. isolates especially in an immunocompromised host should not bedisregarded without a thorough investigation.

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