



# Asymptomatic Pulmonary Cryptococcosis And Tuberculosis Co-infection in an immunocompetent Host: A case report.

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## ABSTRACT

Pulmonary Cryptococcosis is a rare fungal infection that mostly occurs in immunocompromised host. However, with advancement in diagnostic approach like tissue biopsy, cryptococcal infections are now increasingly being recognised.<sup>1</sup> In immunocompetent host, cryptococcal infection is often asymptomatic and rarely becomes disseminated.<sup>2</sup> Symptom development in immunocompetent host largely depends on burden and virulence of pathogen.

Due to similarities in clinical, radiological and pathological findings in Cryptococcosis, Tuberculosis and other fungal infections like Blastomycosis, it is important to have a tissue biopsy to confirm the diagnosis.<sup>3</sup>

The aim of this case report is to highlight the investigation necessary to diagnose both fungal infection and Tuberculosis due to similar clinical, radiological features in both. We report a case of Gene Xpert positive Tuberculosis and histopathology proven Pulmonary Cryptococcus in same patient.



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## INTRODUCTION

Cryptococcus is an encapsulated yeast with more than 30 species distributed in the environment. *C. neoformans* and *C. gatti* are the two species commonly known to cause human disease.<sup>5</sup> Pulmonary cryptococcosis is a rare fungal infection which remains underdiagnosed due to its highly variable clinical presentation. The clinical presentation can be variable from asymptomatic to fever, weight loss, cough, night sweats and difficulty breathing mimicking tuberculosis.<sup>1</sup>

Radiological presentation can be a lobar solitary nodule, multiple nodules in both lungs, pulmonary infiltrates, pleural effusion, hilar lymphadenopathy, lung cavitation.<sup>3</sup> In addition, abnormal radiologic findings in cryptococcal disease including nodules, pulmonary infiltrates, pleural effusions, hilar lymphadenopathy, lung cavitation and osteolytic lesions are also found in Tuberculosis.<sup>5</sup>

Early and correct diagnosis of cryptococcal infection is crucial not only to control pulmonary infection but also to prevent dissemination.

Tissue biopsy for histopathology plays an important role in definitive diagnosis.<sup>6</sup> Direct microscopy using India Ink, Giemsa stain, PAS (Periodic Acid Schiff) stain helps distinguish different fungal infection.<sup>6</sup>

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## CASE REPORT

A 65 years old male, non-smoker, diabetic having stable glycemic control with no history of avian exposure or tuberculosis or contact presented in our OPD with complains of fever, dry cough and weight loss for last 8 months. During this period (april-dec 2022) thorough evaluation for Pulmonary Tuberculosis in another tertiary centre was negative including Gene Xpert in BAL.

On presentation patient had ESR (Erythrocyte Sedimentation Rate) 80mm/hr, CRP (C-reactive protein) 33.6, leucocyte count of 3920cells/Cumm with 63% Neutrophil on December 29,2022.

As shown in figure 3 CT chest, lung window shows bilateral nodular opacities involving apicoposterior and inferior segment in left upper lobe and apical, posterior in right upper lobe. Work up for vasculitis and connective tissue disease including ANCA(Anti-Neutrophil Cytoplasmic Antibody), anti-GBM Ab (Anti-glomerular basement membrane antibody) was negative. Viral serology for HIV, Hepatitis B and C was negative. RA (Rheumatoid factor) and Antinuclear antibody test were negative.

Even after a comprehensive evaluation including a bronchoscopy done for bronchoalveolar lavage(BAL) the results remained inconclusive so, a repeat BAL was planned in our centre. Report was negative for malignant cells and AFB stain was negative for tuberculosis. Sputum work-up for fungal c/s and KOH was also negative. However, BAL for Gene Xpert was awaited.

CT guided biopsy was also done after 2 days of admission. Biopsy report showed necrosis and scattered multinucleated giant cells with ill formed granuloma. Numerous intracellular and extracellular variable sized yeast with narrow angle budding were noted as shown in Figure 1-4. Fungal infection consistent with Pulmonary Cryptococcosis was reported. However AFB stain came out to be negative.

BAL done in our centre showed Gene Xpert positive for Mycobacterium Tuberculosis.

Anti tuberculous medication was started along with antifungal (Tab Fluconazole 400mg OD) planned to be continued for 6 months and 12 months respectively.

During 2 weeks follow up patient had significant improvement in fever and dry cough.

## CXR

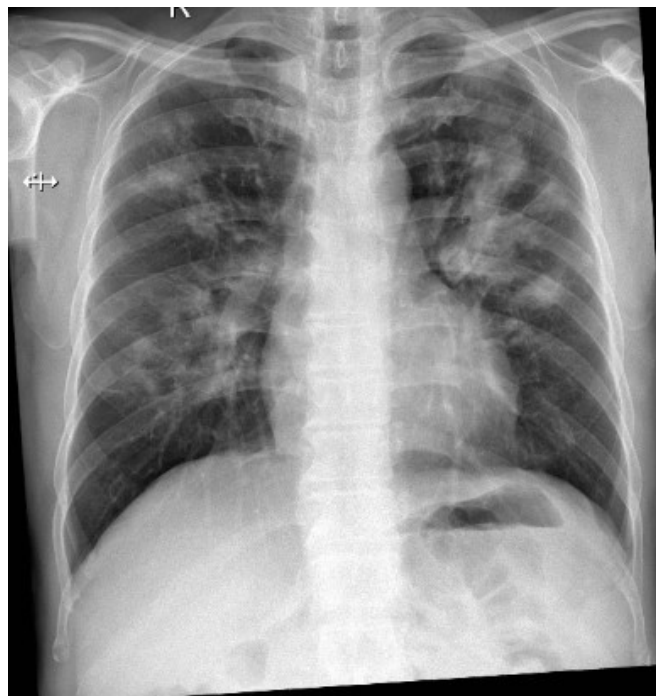


Fig 1: CXR showing bilateral opacities

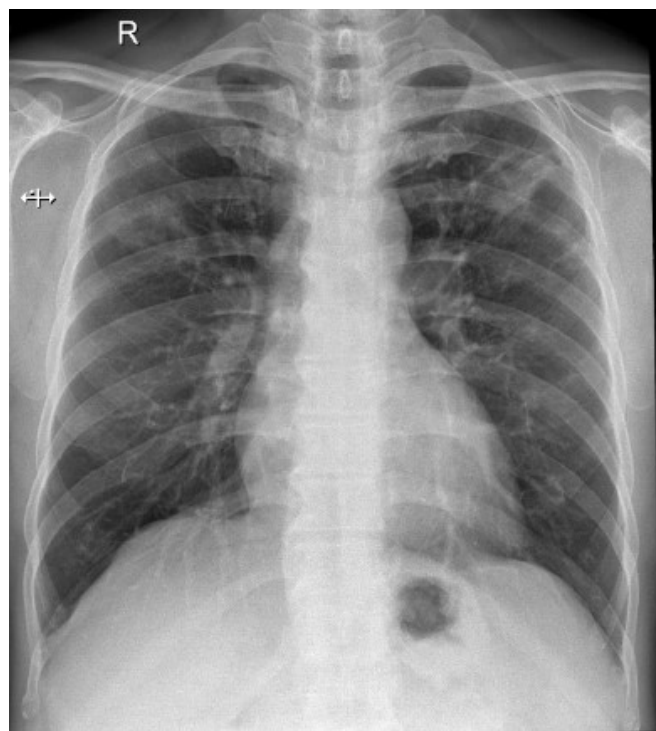


Fig 2: CXR after 4 months of starting treatment showing improvement in bilateral opacities.

## CT CHEST:



Fig 3: CT chest mediastinal and lung window showing bilateral nodular opacities.

Histopathology figure:

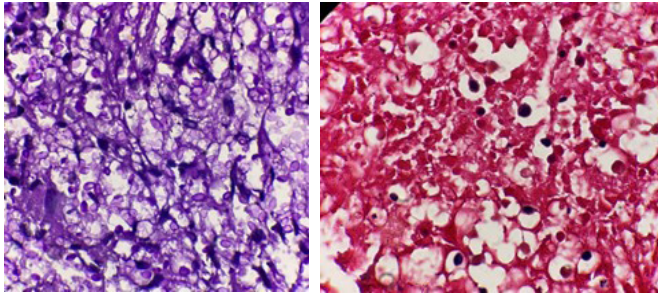


Image 1

Image 2

**Image 1:**(1000x) DPAS stain highlights the yeast forms.

**Image 2:**(1000x)Gram stain highlights the granular material inside the yeast.

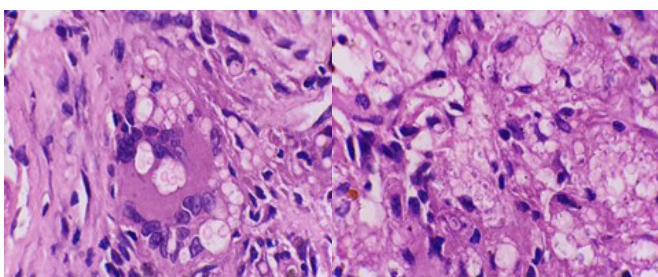


Image 3 and Image 4: (1000x) Scattered multinucleated giant cells along with sheets of histiocytes with numerous intracellular and extracellular variable sized yeast forms

## DISCUSSION

Our patient presented with a chronic cough, fever, and weight loss. Multiple, bilateral nodular densities on chest radiography led to a transbronchial biopsy, which showed innumerable, encapsulated, yeast which led to the confirmation of pulmonary cryptococcosis. Along with Gene X-pert testing positive for Tuberculosis. The clinical presentation along with laboratory findings were consistent for diagnosing a concurrent infection of TB with Cryptococci.

Human to human transmission is not reported. Found abundantly in the droppings of pigeons and other birds,<sup>7</sup> Cryptococcus infection predominantly occurs in immune compromised hosts. However with advancement in diagnostic approach like tissue biopsy, infection in immune competent host is being recognised.<sup>1</sup>

Concurrent infection of Cryptococcosis and Tuberculosis is rarely reported. Co-infection delays diagnosis leading to increased mortality and morbidity in limited resource settings.<sup>4</sup> The similarities in clinical, radiological and pathological findings makes it even more difficult for early diagnosis. Tissue diagnosis is the definitive step in such case.

Radiological presentation may vary from solitary pulmonary nodule, bilateral random distribution of nodule to pulmonary infiltrates.

Advanced non-culture-based diagnostic tests such as galactomannan, beta D glucan, Cryptococcal antigen testing and PCR should be considered during work up for Tuberculosis keeping Fungal infection as an alternative diagnosis.<sup>8</sup>

Definitive diagnosis can be made from tissue biopsy for histopathology. Direct microscopy using India Ink, Giemsa stain, PAS stain can identify Cryptococcosis.

This Co-infection of Cryptococcosis with Tuberculosis has been an overlooked overtime and needs to be considered by both clinicians and microbiologists while managing a patient.

Infectious Diseases Society of America (IDSA) guidelines for treatment of Pulmonary Cryptococcosis in immunocompetent mild to moderate disease includes Tab Fluconazole 400-800mg orally daily for 6-12 months. In severe immunocompromised host induction with Liposomal Amphotericin 3mg/kg/day intravenous or conventional Amphoterecin 0.7-1.0 mg/kg plus flucytosine 100mg/kg/day orally 2-4 weeks. Followed by Fluconazole 400-800mg orally daily maintenance for 12 months.<sup>9</sup>

## CONCLUSION

The aim of this case report is to focus on simultaneous investigation for fungal infection in patients presumed to have Tuberculosis especially in endemic areas. The clinical,



radiological and pathological similarities in presentation can be tricky hence tissue biopsy helps in definitive diagnosis.

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