Invasive Pulmonary Cryptococcal Infection Masquerading as Lung Cancer With Brain Metastases: A Case Report

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Abstract

Background: Cryptococcosis is a global disease problem. Although seen more frequently in the severely immuno-suppressed, it can also be seen in patients without apparent immuno-suppression. Patients with pulmonary Cryptococcosis typically present with cryptococcal pneumonia while brain cryptococcosis present with meningitis.

Case presentation: Here we present our experience in the management of a 33-year-old immunocompetent man, diagnosed of invasive pulmonary Cryptococcal disease with spread to the brain. This case is unique because the patient was previously treated for tuberculosis and presented with typical bronchopulmonary (difficulty in breathing and cough), thoracic (diminished breath sounds and dull percussion notes), extra-thoracic (intra-cranial space occupying lesion) as well as Computed Tommography (CT) Scan features attributable to lung cancer. Diagnosis of Cryptococcosis was made by identification of oval thick-walled yeast on histology of lung biopsy specimen.

Conclusions: We conclude that invasive Cryptococcosis affecting the lung and brain may present with a clinical picture similar to metastatic lung cancer. We recommend routine fungal stains and fungal culture in suspected cases.

Background

Cryptococcus neoformans is an ubiquitous pathogen found in both temperate and tropical regions of the world. It is prevalent in organic matter and soil enriched by animal and bird droppings. It is the 3rd most common invasive fungal infection in transplant recipients and account for 8% of invasive fungal infections. [1][2] About 1 million cases of Cryptococcosis occurs throughout the world & estimated 650,000 associated deaths occur annually.[3] An ecological study from South Eastern Nigeria reported a high incidence of C. neoformans in bird droppings evaluated over a wide geographical area.[4] The spectrum of cryptococcal disease ranges from self-limiting cutaneous infections to fatal systemic infections. Systemic disease is contracted by inhalation of the desiccated yeast which leads to a primary pulmonary infection.[5] This can remain latent for extended periods of time, but can re-emerge and disseminate if the host becomes immunocompromised. Upon dissemination the organism shows particular tropism for the central nervous system, frequently causing fatal meningitis.[6]

Here, we report the case of an immunocompetent young man who presented with features of a right lung mass and Central Nervous System (CNS) manifestations that mimicked a metastatic lung cancer with intra-cranial space occupying lesion. These features contrasted with the typical presentation of Cryptococcal pnemonias and Cryptococcal meningitis.

Case Presentation

A 30-year-old male university undergraduate student from Calabar, presented to the out-patient clinic of Department of Surgery, University of Calabar Teaching Hospital, Nigeria with complaints of recurrent

headache of 1yr duration, progressive weight loss of about 3 months duration, persistent difficulty in breathing & cough of two months duration and dizziness of one-month duration. Prior to presentation, he had been receiving care at a peripheral health care facility.

He described the headache as recurrent, initially frontal but later occipital, throbbing, with radiation to the neck, and associated blurred vision, dizziness, weakness of the left limbs and seizures. The seizures were described as generalized tonic clonic and he had noted four episodes prior to presentation, with each episode lasting less than five minutes.

He complained of intermittent fever, cough which was associated with hemoptysis and he was dyspneic on exertion. He also had right lower quadrant abdominal pain associated with effortless, non-bloody vomiting, anorexia, and non-bloody diarrhea. He did not have any history of failure to thrive, small stature, hypotonia or correction of conotruncal congenital cardiac anomaly that may suggest congenital absence of thymus. There was no history of recurrent pyogenic or viral infections. No history of surgical excision of the spleen. No history of recurrent skin eruptions or sino-pulmonary infections.

He was an undergraduate student, has a history of two pack years of tobacco use and stopped smoking about ten years prior to admission.

He had a history of treatment for pulmonary tuberculosis about two years prior to presentation and had been treated with Isoniazid, Rifampicin, Pyrazinamide and Ethambutol initially for six months and subsequently for eight months when he was thought to have relapsed.

On examination he was cachectic, conscious and ill looking. He was tachypneic, tachycardic and hypertensive with a respiratory rate of about 30 breaths per minute, heart rate of 130 beats per minute and blood pressure of 164/126 mm of mecury. He was febrile with a body temperature of 38.5 degrees Celsius. He had diminished breath sounds and dullness to percussion in the right mid lung zones. He also had a left sided hemiparesis and an associated ataxia.

A chest X – ray showed a large mass in the right middle lung zone extending to the hilum. Further evaluation with computerized tomography (Figure 1) scan confirmed the presence of a mass infiltrating the right upper and middle lung lobes. The mass measured 10 x 10 cm in its widest diameter.

In view of his neurological presentation he also underwent computerized tomography scan of the brain (Figure 2) which revealed a 5x4 cm intracranial mass with perilesional edema and mass effect.

Provisional diagnosis at this time was a metastatic lung cancer with intra-cerebral metastases. Due to lack of a less invasive means, open surgical lung biopsy was done to obtain tissue for histological characterization of the tumour. Histology of specimen obtained revealed the presence of interstitial mononuclear infiltrate, numerous foamy macrophages and granuloma formation with congested capillaries, focal fibrosis and thickening of the interstitial alveolar septa. Lying freely within the tissue were numerous oval shape thick walled yeast form of a fungal organism identified as Cryptococcus neoformans following PAS staining (Fig. 3-6) Fungal culture of pulmonary masses were not routine in our

practice as at the time of management of this patient hence it was not done. Based on the histologic finding of fungal organism identified as Cryptococcus, a diagnosis of invasive cryptococcosis was made.

Other investigations done included complete blood count, metabolic panel and HIV serology, AFB and GeneXpert. These were essentially unremarkable.

He was started on treatment with Flucytosine and Fluconazole initially as Amphotericin B was not readily available. He had this for 7 days. When it became available, he was treated with 14 days of intravenous Amphotericin B before he was transitioned to oral Fluconazole 400mg daily for 8 weeks, then 200mg daily for 6 months. On completion of this treatment, both pulmonary aspirate and CSF cultures were negative for fungal growth however there were residual radiographic abnormalities.

He made significant clinical improvement with resolution of hemiparesis and cerebellar ataxia. He had an ipsilateral empyema thoracis with empyema necessitans and spontaneous bronchopleural fistula 18 months after antifungal treatment. This was managed using closed tube thoracostomy drainage. Culture of the pleural aspirate yielded growth of multi drug resistant Klebsiella sensitive to Amikacin but no fungal growth.

Discussion

Infection with Cryptococcus neoformans generally affects immunocompromised individuals,[7] although cases have been reported in individuals with no apparent underlying immunodeficiency[8]. Most of the cases occur amongst patients with advanced HIV disease, solid organ transplant recipients, patients receiving large doses of exogenous glucocorticoids, cytotoxic chemotherapy or biologic immunomodulating therapies and patients with primary and secondarily acquired immunodeficiency states. A high index of clinical suspicion is necessary in the appropriate clinical setting to facilitate targeted investigation and timely diagnosis.

Here we present the case of a young, HIV negative male who presented with disseminated cryptococcosis confirmed on lung tissue biopsy. He presented with bronchopulmonary (cough and dyspnoea) symptoms which could be ascribed to lung cancer. His additional symptoms of dizziness and ataxia were attributable to intracranial metastases. The finding of intrapulmonary and intracranial masses masqueraded as lung cancer with brain metastases. The clinical presentation of this patient is unusual. He had features of pulmonary mass and intra-cranial space occupying lesion in the absence overt pneumonia and meningitis which are typical features of pulmonary and CNS Cryptococcosis respectively. Management was hampered by a lack of bronchoscopy and Video Assisted Thoracoscopic Surgery (VATS) which necessitated open biopsy procedure in an effort to establish a histological diagnosis. Minimally invasive procedures such as bronchoscopy and VATS could have prevented open thoracotomy for biopsy which is a major surgery. This practice of open thoracotomy for biopsy of lung masses, is not unusual in many health facilities in low- and middle-income countries.

Although seen more in severely immunocompromised patients, cryptococcosis can be seen in patients without apparent immunosuppression.[9] It has been suggested that with the increasing availability of highly active antiretroviral therapy, non-HIV-infected individuals may become the predominant infected group.[8] The virulence of Cryptococcus is related to its polysaccharide capsule as well as the presence of specific enzymes including laccase, phospholipase B and inositol phosphosphingolipid-phospholipase and presence of melanin and mannitol which is correlated with increased resistance to osmotic, heat, and oxidative stress.[6,10]

In the lungs, Cryptococci replicate and synthesize a large polysaccharide capsule, which protects against phagocytosis. The Cryptococci that are successfully phagocytosed reside and replicate in mature phagolysosomes and subsequently spread to other cells using multiple mechanisms. In response to Cryptococci there is a type 1 helper CD4+ T cell response. CD4+ T cells are necessary to prevent dissemination from the lungs and both the CD4+ and CD8+ cells are required for clearance of infection in mice.

The lung is the most commonly involved primary site and the central nervous system is the most common site of dissemination. Pulmonary involvement ranges from asymptomatic colonization to multifocal consolidation and even the acute respiratory distress syndrome. In immunocompetent hosts, most pulmonary infections are asymptomatic or mildly symptomatic and may even be found incidentally on imaging. It can also cause latent lung infection and disseminate when cellular immunity is depressed.

In the immunocompetent host, acute infection may present as a pneumonia manifesting with fever, fatigue, cough, and sputum production.[11] In immunocompromised patients, severe symptoms including fever, cough and shortness of breath are key manifestations. In humans, C. gatti causes predominantly meningoencephalitis.[10]

A multicenter retrospective study of pulmonary cryptococcosis from China reported pulmonary cryptococcosis as the third most prevalent fungal lung infection in their series.[8] Interestingly most of their patients had no apparent underlying disease much like our index patient. Our patient also had a history of previous treatment for pulmonary tuberculosis. This calls to question if the pulmonary Cryptococcal and tuberculous infections were a co – infection or a sequential infection. Pulmonary Cryptococcal and Tuberculous co – infection in a patient on anti – retroviral therapy has been reported in a Nigerian patient.[7] It would appear that our patient presented at a very late stage of his illness with a large mass causing respiratory distress alongside neurological features most likely due to the space occupying Cryptococcoma noted on brain computerized tomography scan.

Pulmonary cryptococcosis can have a variety of radiological features. CT features commonly reported include solitary or multiple pulmonary nodules which could be smooth or speculated.[12] It could also present as focal or multifocal airspace consolidation[13] in the immunocompetent, while cavitation and the presence of the halo sign are more commonly seen in immunocompromised hosts.[14] Our patient did not have these typical CT features. Liu et al[8] had noted that pulmonary lesions were mainly seen in

the peripheral lung fields, we had a lesion that spanned the breath of the hemithorax with infiltration of the chest wall.

Regarding treatment, the choice of therapy depends on the immune status of the host and the presence of extrapulmonary infection. In severe cases with dissemination the treatment is divided into three phases namely induction, consolidation and maintenance regimens.[15] Induction is commonly achieved with intravenous amphotericin B deoxycholate 0.7-1mg/kg/day and Flucytosine 100mg/kg/day. The consolidation and maintenance phase are achieved with 400-800mg/day and 200-400mg/day respectively. Mild to moderate infection is treated with fluconazole 400mg/day for 6-12 months. Patients with asymptomatic resected solitary nodules, undetectable serum cryptococcal antigen and no evidence of extrapulmonary infection may be observed closely without necessarily instituting antifungal therapy.

Our index patient received Flucytosine and Fluconazole and then Amphotericin B as this was not readily available initially.

John F. Fisher[9] raised the following questions about Cryptococcosis in the immunocompetent patient: (i) Does symptomatic pulmonary cryptococcosis resolve in most individuals without antifungal therapy? (ii) Does asymptomatic pulmonary cryptococcosis resolve in most individuals without antifungal therapy? (iii) Does antifungal therapy hasten clinical and radiographic resolution of pulmonary disease in both symptomatic and asymptomatic individuals? (iv) How often can negative fungal cultures be expected when pulmonary tissues or secretions reveal encapsulated yeast and what is their significance? (v) Can antifungal therapy be discontinued despite the presence of significant radiographic abnormalities? (vi) How long do pulmonary lesions persist with and without therapy? (vii) What is the significance of persistently positive serum cryptococcal antigen testing with pulmonary cryptococcosis? We are unable to answer all the above questions based on experience with this patient however, we note that discontinuation of antifungal treatment with negative culture despite residual radiographic abnormalities did not result in recurrence of fungal pathology during the 3-year follow up of this patient. We have placed our index patient on close follow up because we think the lung lesion that accounted for the residual radiographic abnormality may be a nidus for bacterial infection. This may also have accounted for the occurrence of bronchopleural fistula during the follow up period. Following the experience gained from the management of this patient, we have lowered our threshold for fungal studies on lung biopsy specimen.

Conclusions

Pulmonary cryptococcosis may have intracranial dissemination. This may give rise to radiological findings in the lung and brain masquerading as a metastatic lung cancer. Residual radiological lung findings after adequate antifungal therapy was not associated with a recurrence of invasive fungal infection but may be associated with occurrence of bacterial complications such as empyema and bronchopleural fistula. We recommend a high index of suspicion and when applicable, include fungal panel among special stains for lung biopsy specimen.

Abbreviations

CT: Computed Tomography

VATS: Video Assisted Thoracoscopic Surgery

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Authors' contributions:

CPE – Was the lead surgeon during the biopsy, wrote the manuscript and approved the final copy of the manuscript.

CIN – Directly involved in the care of the patient. Reviewed the manuscript and approved the final copy

SOO - Directly involved in the care of the patient. Reviewed the manuscript and approved the final copy

NJE - Directly involved in the care of the patient. Reviewed the manuscript and approved the final copy

EAO – Undertook the microbiologic studies. Reviewed the manuscript and approved the final copy

PJ - Undertook the histopathologic studies. Reviewed the manuscript and approved the final copy

AUE – was the supervising consultant Reviewed the manuscript and approved the final copy

OOB - Was the supervising consultant. Reviewed the manuscript and approved the final copy

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Figures

Figure 1

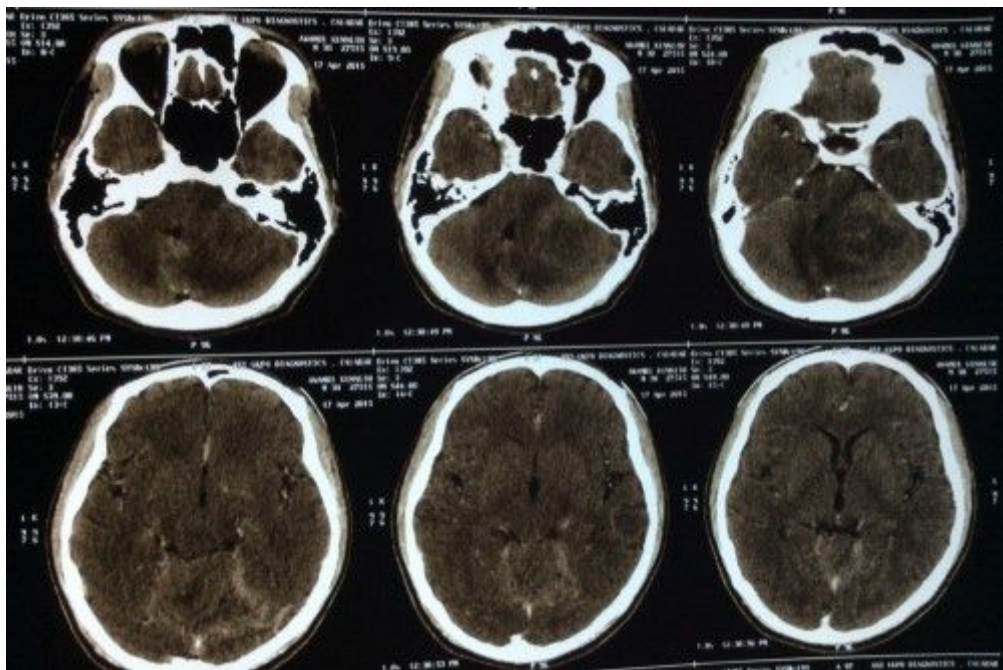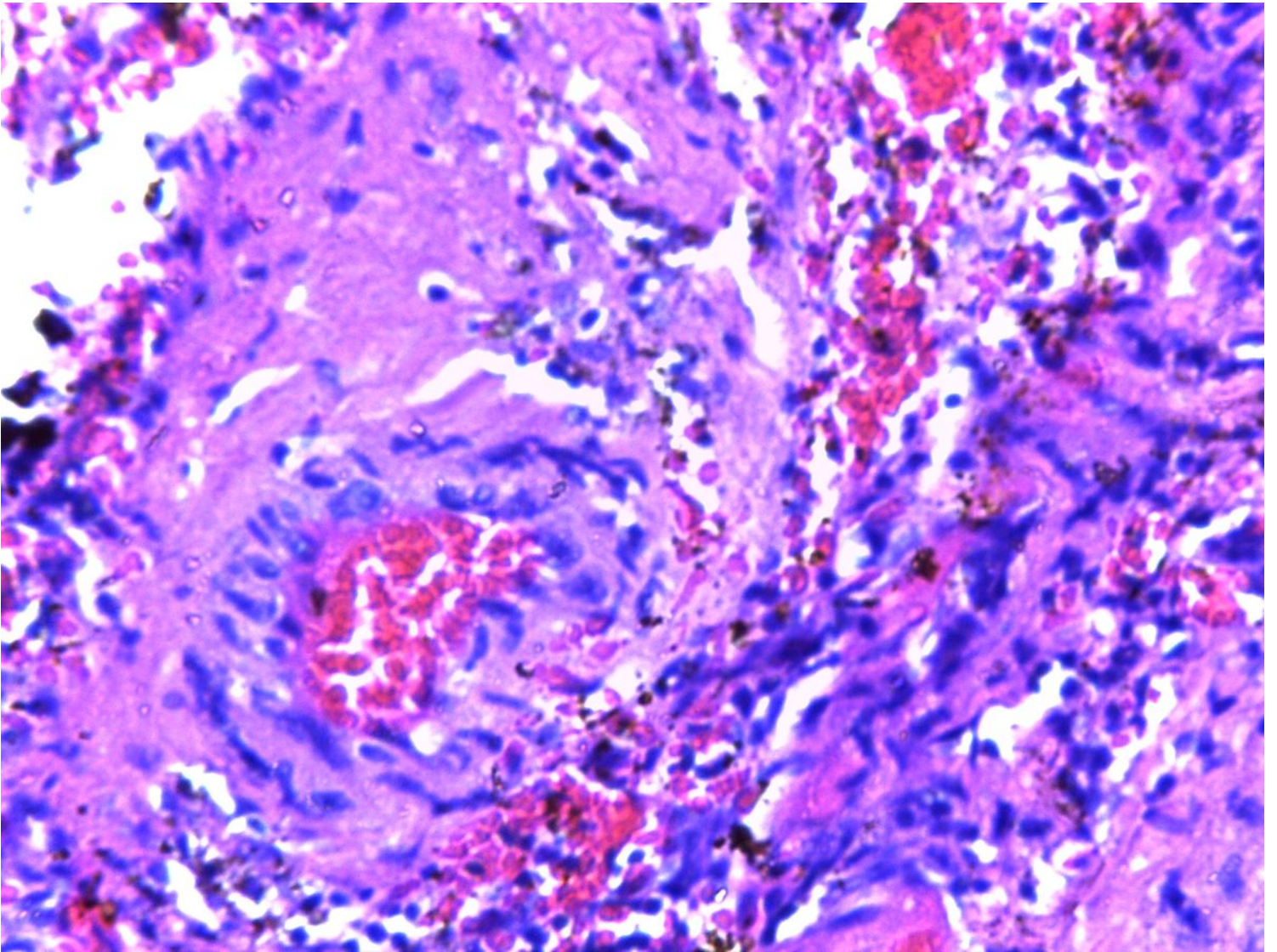computerized tomography

Figure 2

Brain CT

Figure 3
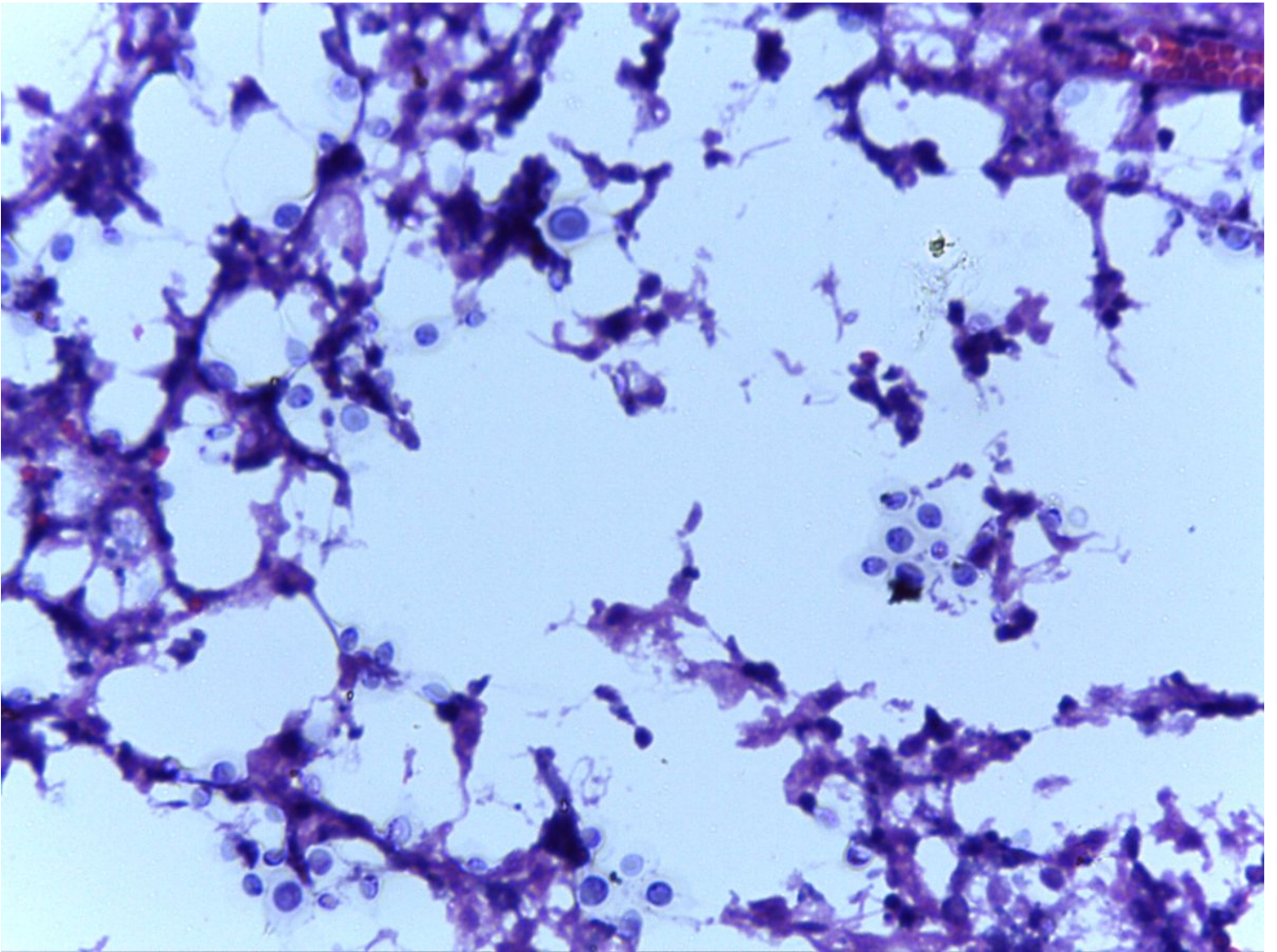
Figure 3 shows Mononuclear in filtrate original

Figure 4

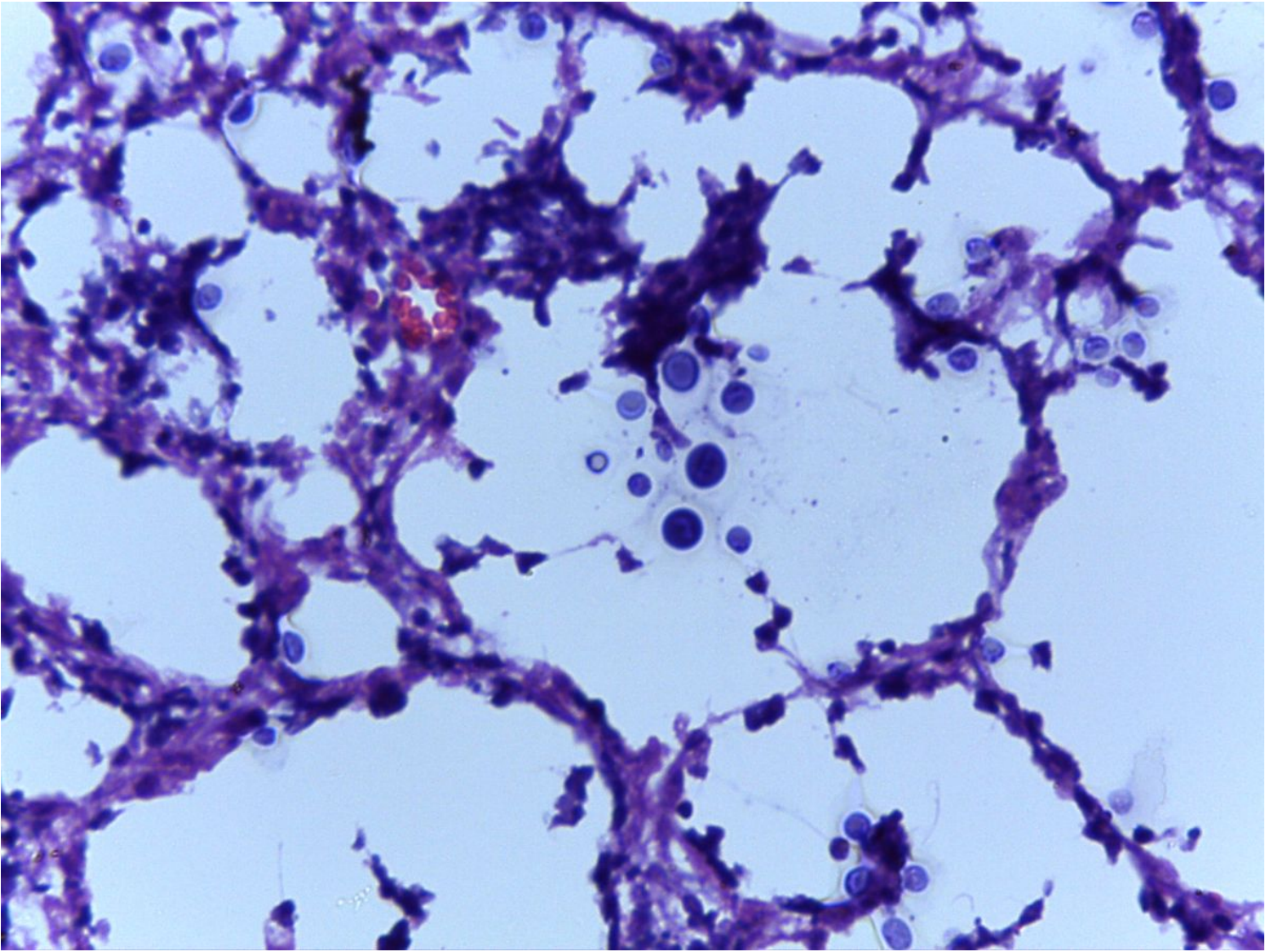Figure 4 shows prescence of yeast original

Figure 5

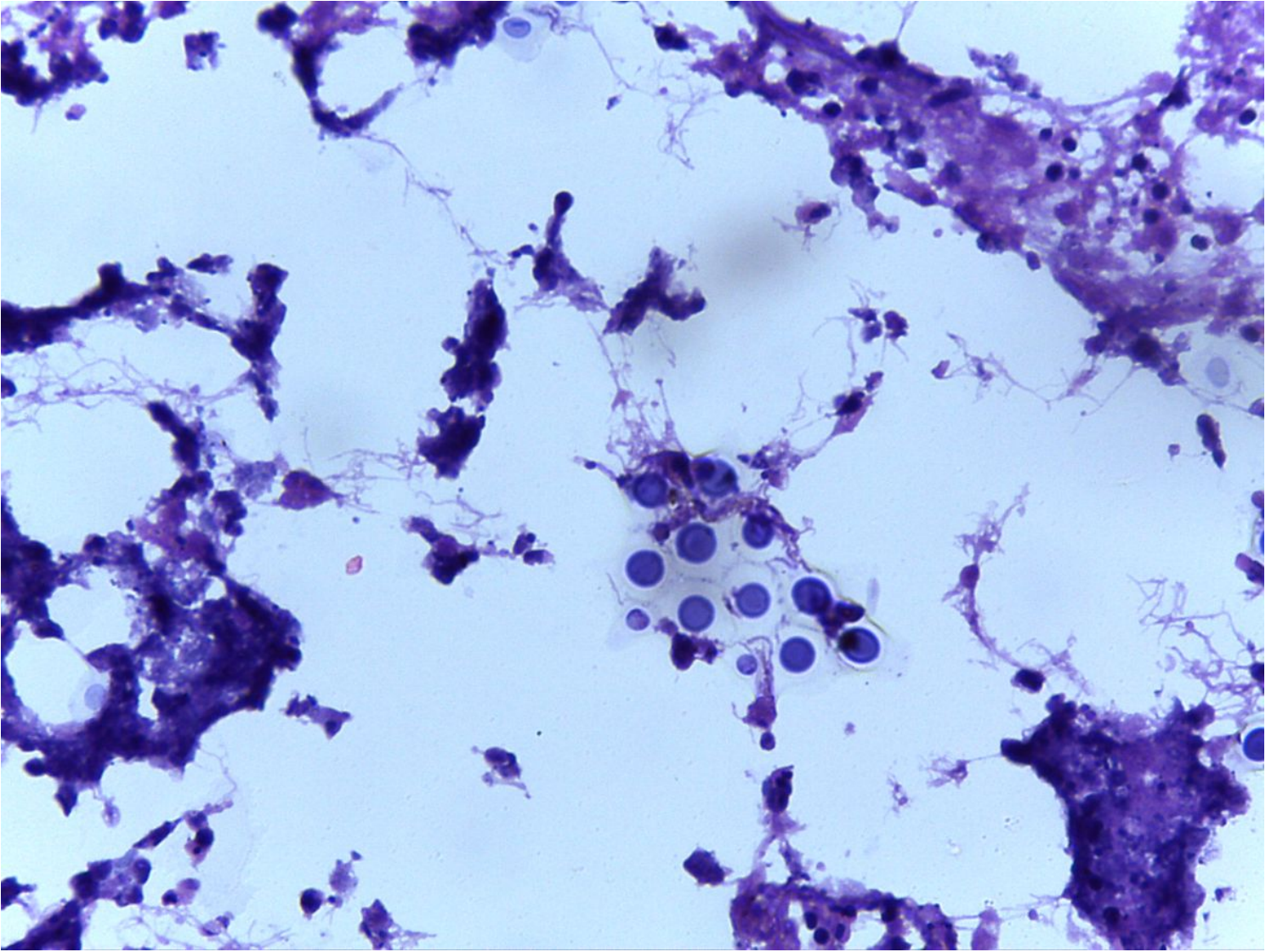Fig 5 shows relationship of yeast with alveali

Figure 6

fig 6 shows identifying oval shaped thick walled yeast

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