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Fatal Pulmonary Infection by a Multi-Resistant Strain of C.Laurentii in a Patient with Active Pulmonary Tuberculosis

Aikaterini Marini [α], Alexios S. Antonopoulos [σ], Claudia Lakoniti [ρ], Evangelia Kouskouni [ω], & Konstantinos Gerolymatos [¥]

Abstract- We report the first case of concomitant *C. laurentii* and *M. tuberculosis* pulmonary infection in a non-immunocompromised patient caused by a multiresistant C.laurentii strain and the fourth reported case of *C.laurentii* pulmonary infection up to now. We review the literature regarding *C. laurentii* pulmonary infections as well as its treatment.

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I. Introduction

Our knowledge regarding non-neoformans cryptococcal infections has dramatically changed over the last years. While non-neoformans cryptococci had been previously considered as simple saprophytes, we now know that such cryptococci can be occasional pathogens, responsible for serious infections. *C.laurentii* together with *C.albidus* account for more than 80% of non-neoformans cryptococcal infections [1]. To our knowledge this is the fourth case of human *C.laurentii* lung infection and the first report of tuberculosis and *C.laurentii* co-infection of in a non-immunocompromised patient.

II. Case Report

An ex-tanner, 83-year-old man presented to our emergency department with a 2-week history of weakness, chills, dyspnea, productive cough, haemoptysis and fever up to 39.5°C. He had a history of arterial hypertension, COPD, chronic atrial fibrillation and had undergone a surgery for an in-situ large intestine tumor removal 6 years ago. Physical examination revealed respiratory distress (35 breaths / min), with ample crackles and wheezes on auscultation of both lungs, while chest x-ray revealed signs of left-upper lobe pulmonary infiltration. The patient was hemodynamically stable, however his arterial blood gases indicated mild hypoxemia (pO2=62mmHg, pCO2=42mmHg, SaO2=89%). The initial laboratory tests revealed an acute inflammatory status with leukocytosis (WBC=15390/μL, Neutrophiles=13670/μL), a three-digit erythrocytes sedimentation rate (ESR=119mm/h) and highly elevated C-reactive protein (CRP=292 mg/L). There were no laboratory findings of renal / liver impairment or electrolytes' abnormalities. Blood, urine and sputum cultures were obtained and a tuberculin test was performed. He was immediately treated with ceftriaxone (2g/day), bronchodilators and nasal oxygen as a possible lung infection.

The combination of positive tuberculin test (15mm) and the radiologic and clinical features indicated a high risk of tuberculosis infection (figure 1A). Chest computed tomography reinforced our initial suspicion of active pulmonary tuberculosis by revealing a cavitated opaque lesion of the left upper lobe, as well as bronchopulmonary infiltrations of the lower lobes in both lungs and the reed (figure 1B). On this basis anti-tuberculosis treatment was initiated (rifampin 600mg/day, isoniazid 300/day, ethambutol 2g/day and pyrazinamide 2g/day). The patient remained nonfebrile for the next 9 days and the clinical and laboratory findings were ameliorated (WBC=7340/μL, Neutrophiles=6010/μL, CRP=94.5mg/L, ESR=95 mm/h). Meanwhile two samples of blood and sputum cultures were obtained.

However, during the following days the patient's clinical state deteriorated, manifesting marked respiratory distress, tachypnea, fever accompanied with chills (up to 39.0°C) and lethargic mental status. Moreover there was a simultaneous alteration in laboratory findings (CRP=170mg/L, ESR=102mm/h). Blood and urine cultures were negative, while sputum cultures' analysis revealed *M. tuberculosis* suggesting active pulmonary tuberculosis. Furthermore, sensitive strains of *Klebsiella pneumonia* and *Citrobacter freundii* were also isolated in sputums as well as a rare strain of Cryptococcus, identified as *C. laurentii*. These findings suggested co-infection of the underlying pulmonary tuberculosis with a very rare and highly resistant type of non-neoformans Cryptococcus. For the newly isolated bacterial strains, ciprofloxacin (400mg x 2) was added based on the antibiogram's results. Importantly, the

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identified *C.laurentii* strain was multi-drug resistant to all known antifungal agents (amphotericin B: MIC>16000 μg/mL, fluconazole: MIC>129000 μg/mL, itraconazole: MIC>4000 μg/mL, voriconazole: MIC>8000 μg/mL). Given the above results, empiric antifungal treatment with liposomial amphotericin B (5mg/kg) and caspofungin (70 mg on the first day and 50mg/day subsequently) was initiated in addition to the anti-TB drugs. The aforementioned multidrug resistance of the isolated Cryptococcus strain was also confirmed by the second sputum culture analysis. A microscope image of the *C.laurentii* strain was also taken and is depicted in figure 2.

Despite treatment, the patient remained lethargic and febrile with deteriorating vital signs. A second CT scan depicted the presence of liquid in pre-existing pulmonary cavity and "ground glass" sign in the right upper lobe (figure 1C). No abnormal findings were observed in the brain and abdomen CT scan. Ultimately the active pulmonary disease led to respiratory failure and death after 23 days of hospitalization.

III. Discussion

Cryptococcus yeast is responsible for a series of very rare and life-threatening fungal infections in immunocompromised patients [2,3]. Cryptococcal infections are usually attributed to neoformans species, distributed in the air, soil, animal and plant organic residues [4]. *C. laurentii* along with *C. uniguttulatus*, *C. albidus*, *C. curvatus* and *C. humicolus* belong to non-neoformans cryptococci. *C. laurentii* and *C. albidus* are responsible for 80% of the non-neoformans infections [1]. Neoformans and non-neoformans species differ in capsule formation, melanin growth and antifungal resistance but their distinct classification remains a matter of debate.

Non-neoformans cryptococci were thought to be saprophytic and nonpathogenic to humans but incidence rates have importantly increased nowadays [1, 5, 6]. Interestingly, there are only 20 cases of *C. laurentii* human infections and only 3 affecting the lungs in immunosuppressed subjects [3, 6-9]. The yeast has been detected in normal skin, air, water, wood, soil, pigeon excrements, cheese, fruits, pork products, bean, wine andmilk of suffering from mastitis cows [10]. There have been no previous reports of *C. laurentii* lung infection in a non-immunocompromised subject neither of a co-infection with *M. tuberculosis*. Thus, the present case is of high clinical interest since we report a unique so far concomitant lung infection of *C. laurentii* and *M. tuberculosis* in a healthy subject.

Predisposing factors to *C. laurentii* infection are the presence of invasive devices (e.g. intravenous catheters, parenteral nutrition), the use of broad spectrum antibiotics, impaired cell-mediated immunity, leukemia, cancer, diabetes mellitus, HIV, prematurity, neutropenia, lymphopenia, immunosuppressive drug use and organ transplantation [1]. Extremely rare cases of "idiopathic CD4 deficiency" and congenital immunodeficiency have been also regarded as responsible for such infections. Our patient had no known defense impairment but he was diabetic and during his hospitalization he was treated with broad spectrum antibiotics. Furthermore, he carried central intravenous catheters for parenteral nutrition purposes.

Infection usually is acquired via the respiratory routes, alimentary tract and injured skin. C. laurentii may cause pneumonia, meningitis (2-9%), peritonitis, cutaneous infection, eye infection, invasive disease or fungemia. Fungemia of *C.laurentii* occurs mainly in cancer patients, neonates or as a complication of immunosuppressive therapy [1,11].

Pulmonary infection of *C. laurentii* can present as pneumonia, lung abscess or empyema [1, 8]. Typical radiographic findings include opaque or cavitated lesions, hilar enlargement, pleural fluid or an ARDS like pattern [1]. In our case, the chest radiography and a chest CT scan revealed a cavitated lesion with liquid levels and a typical pattern of pneumonia. Furthermore, the yeast has been previously isolated from sputum, pleural or abscess fluid and bronchial swab material [1]. Thus, its identification in sputum is regarded as a reliable one.

Pulmonary or oropharynx *C. laurentii* infection is rare and has been recorded only in immunity defense-impaired patients [3]. Only a previous *C. laurentii* lung infection has been reported in a subject with unknown underlying disease and two cases of *C. laurentii* presence in cadavers belonging to non-immunosuppressed subjects, where there was also a co-infection with *C. neoformans* strains. Our patient presented pulmonary *C. laurentii* infection which is the first reported in a living non-immunocompromised subject.

Additionally, this is the first case of simultaneous pulmonary infection of *C. laurentii* and *M. tuberculosis* in otherwise healthy or non-immunosuppressed subjects. Concomitant cerebral tuberculosis and cryptoccocosis are extremely rare in the literature, affecting only HIV patients [3].

There is no standard treatment for C. laurentii infection. In a number of series, *C. laurentii* has been successfully treated with amphotericin B (94%) or fluconazole [8]. In vitro evidence about the susceptibility of *C. laurentii* to antifungal agents, suggests that *C. laurentii* strains are mainly sensitive to amphotericin B and itraconazole. Itraconazole, ketoconazole and voriconazole are scarcely preferred, though itraconazole has better tissue bioavailability in lungs compared to fluconazole. Fluconazole is strongly indicated for fungemia due to *C. laurentii*. Drug susceptibility testing should be conducted before any commence of

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treatment. Antifungal resistance is associated with melanin deposition of the strains [12] and is referred mainly for fluconazole and flucytosine. It has been also related to prior azole administration and other host comorbidities [1]. Nevertheless, in a previous study testing drug susceptibility of yeasts found in synanthropic bird faecal samples, *C. laurentii* was found highly resistant in 11 antimycotic agents [10]. *C. laurentii* found in our patient was also highly resistant to all common antifungals (fluconazole, amphotericin B, itraconazole, voriconazole). Importantly, this evidence highlights that these rare infections can be severe and even fatal, due to our inability to efficiently combat with these highly resistant *C.laurentii* strains. Apart from resistance to antifungal agents, advanced age and CNS involvement have been identified as poor prognostic factors [1].

The current report describes the first case of *C. laurentii* concomitant lung infection with *M. tuberculosis* in a non-immucompromised patient. *C. laurentii* has recently been recognized as an opportunistic fungal pathogen in immunosuppressed subjects but remains extremely rare in healthy subjects. Early suspicion and diagnosis are critical to prompt treatment. It is critical to remain vigilant for Cryptococcosis lung infections even in non-immunosuppressed patients as they may lethal and mimic other lung diseases.

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Figures and Figures Legends

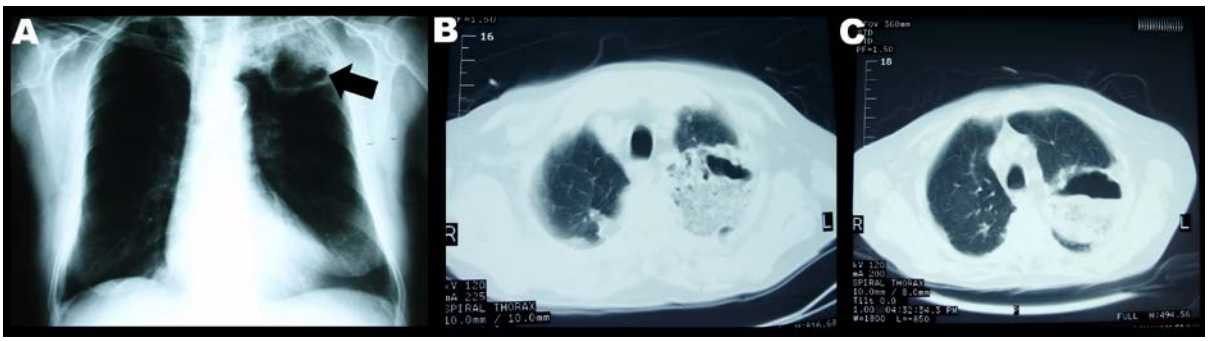

Figure 1 A : Posteroanterior chest radiograph shows left upper lobe consolidation and a cavitary opacity in the left upper lobe, **B.** Chest CT revealing caseous necrosis and ground glass opacities in the left upper lobe, **C.** Chest CT revealing a cavity with irregular borders and air-fluid levels, secondary to caseous necrosis, surrounded by thick outer wall

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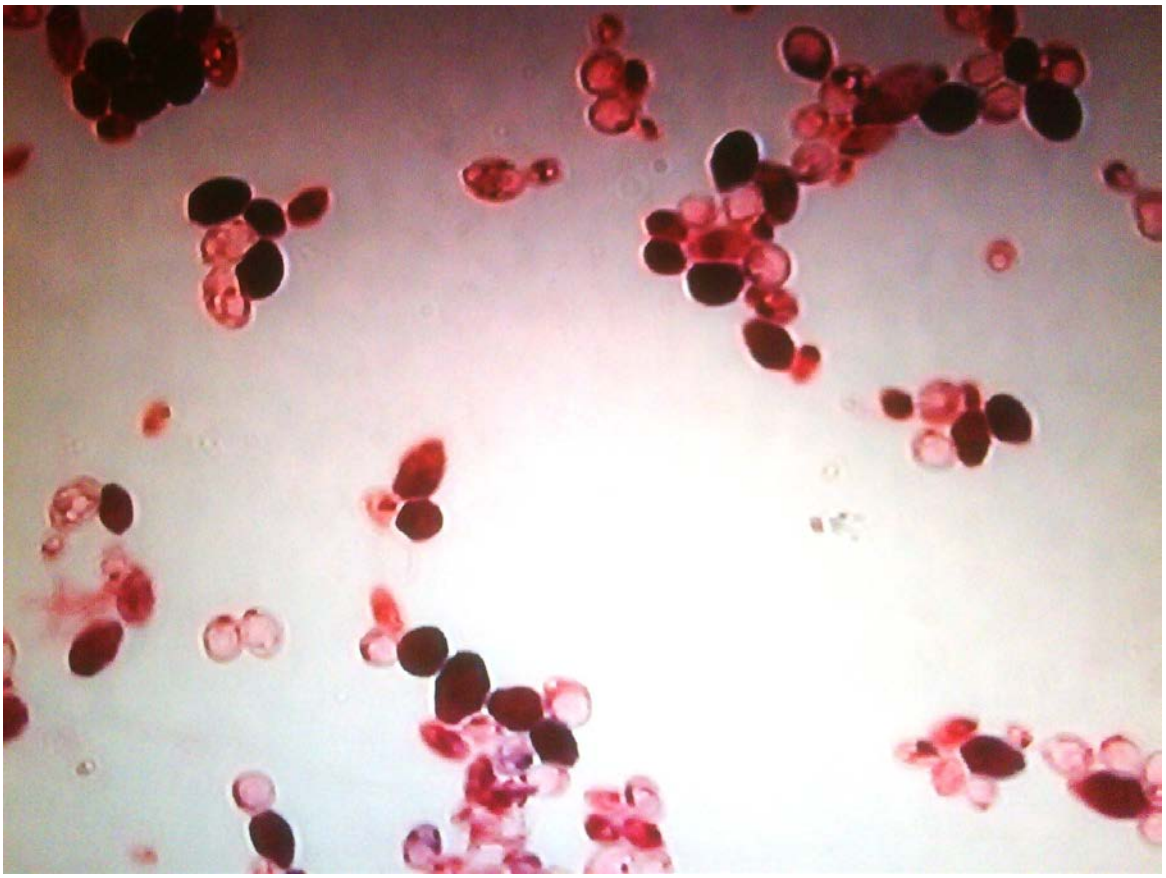

Figure 2 : The Gram's stain revealed spherical and elongated budding yeast-like cells without any pseudohyphae, identified as *C .laurentii*. India ink was also used for early visualization of the capsule that gave the characteristic "halo" around the cell (not shown here)

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