**Mycobacterium tuberculosis/Cryptococcus neoformans Co-Infection in an Immunocompetent Non-HIV Patient**

Salma Albahrani1, Donya Al Hassan2, Yusuf Vapra3, Saad Alsubaiae4 and Amal Shilash4*

1Department of Internal Medicine, Infectious disease section, King Fahd Military Medical complex, Dhahran, Eastern Province, Kingdom of Saudi Arabia
2Department of Radiology, Cardiothoracic section, King Fahd Military Medical complex, Dhahran, Eastern Province, Kingdom of Saudi Arabia
3Department of Internal Medicine, Pulmonology section, King Fahd Military Medical complex, Dhahran, Eastern Province-Kingdom of Saudi Arabia
4Department of Histopathology, King Fahd Military Medical complex, Dhahran, Eastern Province, Kingdom of Saudi Arabia

1Corresponding author: Amal Shilash, Department of Infection Control, King Fahd Military Medical complex, Dhahran 31952, Eastern Province, Kingdom of Saudi Arabia, Tel: 00966509986630; E-mail: amalsalshammar@gmail.com

Received: 21 May, 2020 | Accepted: 17 Jun, 2020 | Published: 24 Jun, 2020


**Copyright:** © 2020 Albahrani S, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

**Abstract**

**Background:** Tuberculosis and cryptococcosis co-infection usually occurs in immunocompromised patients with impaired cell-mediated immunity. Here, we report a case of disseminated tuberculosis with co-existing pulmonary cryptococcosis in a non-HIV patient. However, there is a history of preceding exposure to anti-tumor necrosis agents.

**Methods:** The method consists of a retrospective descriptive analysis of a single case as a case report.

**Results:** A 62-year-old Saudi female presented to the Emergency Department (ED) with complaints regarding the two-month history of appetite loss and shortness of breath. Her past medical history showed a history of receiving anti-tumor necrosis factor for Psoriasis nine months before the onset of the symptoms. The chest Computed Tomography (CT) showed bilateral diffuse micro-nodules in the lungs. Therefore, Lung nodule biopsy was done and showed epithelioid cell granuloma and fungal elements of yeast. Positive staining for both Periodic Acid-Schiff (PAS) stain and Gomori Methenamine Silver (GMS) stain. The latter is suggestive of Histoplasmosis which is not endemic in Saudi Arabia. The molecular identification came back as Cryptococcus neoformans. Furthermore, bronchoalveolar lavage was done and a follow-up test with polymerase chain reaction showed Mycobacterium tuberculosis. During her course of admission, the patient had abnormal myoclonic movements. Brain MRI showed ring-enhancing lesions in bilateral basal ganglia. Moreover, the cryptococcal antigen was negative in Cerebral Spinal Fluid (CSF) and positive in serum testing. According to these findings, disseminated tuberculosis in the lung and brain was suspected with pulmonary cryptococcosis where antimycobacterial therapy and anti-fungal were initiated. After two months in therapy, the patient improved.

**Conclusion:** Clinicians should be aware that tuberculosis co-infection with cryptococcosis can co-exist in non-HIV patients without underlying diseases, although it is rare.

**Introduction**

Tuberculosis and cryptococcosis co-infection usually, albeit uncommonly occurs in immunosuppressed patients with impaired cell-mediated immunity or HIV-positive patients [1]. However, there are few reported cases about such co-infection in non-HIV patients without underlying diseases [1]. Here we report a case of disseminated tuberculosis with co-existing pulmonary Cryptococcosis in an immunocompetent patient. The diagnosis was concluded based on bronchoalveolar lavage and brain abscesses following lung biopsy for Cryptococcus neoformans. There is evidence that both Mycobacterium tuberculosis and Cryptococcus neoformans may have suppressive effects on the host immune system which might explain the co-infection in healthy individuals [2].

This case report expands our standing of these infections in an individual with a history of treatment by anti-TNF nine months prior to the clinical presentation.

**Case Presentation**

A 62-year-old Saudi female presented to the emergency department (ED) complaining of a two-month history of loss of appetite, weight loss of about ten kilograms, and periodic subjective fever. Also, she gave a history of shortness of breath and productive cough of whitish
The patient started treatment with anti-fungal agents after lung biopsy, regardless of the impression of histoplasmosis that was not endemic in Saudi Arabia. The choice for liposomal amphotericin 5 mg/kg was chosen based on the brain lesions, and the azoles drugs were avoided because of hepatotoxicity of the anti-TB agents that the patient exhibited. However, during treatment, the patient exhibited mild improvement only and showed drug-induced elevated liver enzymes with a mixed pattern. Therefore, the anti-TB medications were discontinued. Later, the bronchoscopy was repeated and showed positive MTB/RIF PCR gene expert and AFB smear and culture resulted as positive for Cryptococcus neoformans. Further stating with mucicarmine stain that showed clear encapsulated yeast. Antituberculosis regimens (isoniazid, rifampicin, ethambutol, and moxifloxacin) were resumed gradually and with more caution this time. Dexamethasone was added, and step down therapy of fluconazole was initiated. Also, a lumbar puncture was performed to assess the cerebrospinal fluid (CSF) and the AFB smear and culture. The MTB/RIF PCR was negative, and the India ink stain test was negative. The
Figure 2: Mediastinal window shows mild mediastinal and right axillary lymphadenopathy. Also, mild enlargement of the spleen.

Figure 3: Follow up CT demonstrates a progressive enlargement of pulmonary nodules, few of which started to form central cavitations.

Figure 4: Mediastinal window reveals interval calcifications of the right axillary large lymph nodes and numerous foci of calcifications throughout the spleen.

Figure 5: MRI brain shows ring enhancing lesions.

Figure 6: The Grocott methenamine silver stain reveals well fungal elements in black color (×100).

Figure 7: Thick mucinous bright red capsule with mucicarmine stain (×100).

Figure 8: The Grocott methenamine silver stain reveals well fungal elements in black color (×100).

Figure 9: CT chest show marked improvement of the cavitating lung nodules.

other CSF parameters were as follows: the opening pressure was normal, the total white blood cell count was of 2, the protein level was of 0.473 g/l (0.15-0.45), and the glucose level of 5.1 mmol/l (115-130), with serum glucose 12.2 mmol/l. serum Cryptococcal Ag 1:256 positive, but the results were negative from the CSF sample. Further testing included: HIV 1 and HIV 2 serologies, which were all negative. The patient CD4 counted 377 /MI (1000-2800), and the repeated one was 1200/MI (Table 1).

Interpretation of lymphocytes subsets: helper cell count unremarkable, suppressor cell count exceeding reference range. The low CD4/CD8-ratio is detectable in immunocompetent patients with systemic infections: virus, intracellular bacteria, or parasites.

*Mycobacterium tuberculosis* susceptibility isolate came to be fully sensitive to the four standard drugs. The patient was successfully treated with a combination therapy of anti-TB therapy and anti-fungal therapy. She improved clinically and radiologically as per figure 9 and 10.

**Discussion and Conclusion**

Concomitant tuberculosis and cryptoccocosis have rarely been reported in HIV-infected individuals[3]. The co-infection of tuberculosis and cryptoccocosis in immunocompetent individuals appears to be an even-rarer entity [4]. Important underlying diseases that are common to patients with pulmonary tuberculosis and cryptoccocosis include immunodeficiency syndromes such as AIDS, kidney diseases, blood diseases, and cancer. Also, the proportion of such patients receiving corticosteroid treatment or immunosuppressive agents is high. There are several proposed mechanisms of immune deficiency in patients receiving anti-TNF therapy. TNF-α is essential for the formation and maintenance of granulomas [5,6]. As its inhibition can lead to increased risk of new tuberculosis infection, reactivation of latent tuberculosis, and can predispose to other granulomatous infections, such as *Histoplasma capsulatum* [7]. However, histoplasmosis is not endemic in Saudi Arabia [8]. A previous study that examined the soil of multiple cities in Saudi Arabia proved this [9]. TNF-α plays a role in macrophage activation and differentiation and phagosome formation and is critical for the clearance of intracellular pathogens (e.g., *Listeria, Legionella, Salmonella*) [5]. Subsequently, anti-TNF administration can predispose one to opportunistic infections such as *Candida or Aspergillus* because it causes neutropenia [10]. TNF-α is also crucial for immune responses against viral pathogens, and its inhibition could predispose to the Hepatitis B Virus (HBV) [11] or Varicella-Zoster Virus (VZV) [12]. *C. neoformans* and *M. tuberculosis* infections are believed to be acquired through inhalation of aerosolized particles from the environment. Primary pulmonary tuberculosis is thought to be a latent infection in many cases. Pulmonary tuberculosis in elderly patients may be etiologically associated with reactivation of a latent pulmonary infection. However, the mechanism of cryptococcosis onset is still unclear. Several possibilities have been considered, including primary progression, reactivation, and reinfection [13]. Our case appears to be one of the few reported

**Table 1:** Patient is considered immunocompetent based on the following findings.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Results</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocytes, absolute count</td>
<td>2143/ul</td>
<td>1000-2800</td>
</tr>
<tr>
<td>T- lymphocytes (CD3+)</td>
<td>1542/ul</td>
<td>700-2100</td>
</tr>
<tr>
<td>T- lymphocytes (CD3+)</td>
<td>73%lymph</td>
<td>55-83</td>
</tr>
<tr>
<td>T - helper cells (CD3+/CD4+)</td>
<td>434/ul</td>
<td>300-1400</td>
</tr>
<tr>
<td>T - helper cells (CD3+/CD4+)</td>
<td>20-%lymph</td>
<td>28-57</td>
</tr>
<tr>
<td>T - suppressor cells (CD3+/CD8+)</td>
<td>1107+ /µl</td>
<td>200-900</td>
</tr>
<tr>
<td>T - suppressor cells (CD3+/CD8+)</td>
<td>52+ %lymph</td>
<td>10-39</td>
</tr>
<tr>
<td>CD4+/CD8+ ratio</td>
<td>-0.39</td>
<td>1.0-3.6</td>
</tr>
</tbody>
</table>

**Table 2:** Reported case of co-infection tuberculosis and cryptoccocosis in non-HIV patient without underlying diseases.

<table>
<thead>
<tr>
<th>Case/Ref</th>
<th>Age / Sex</th>
<th>Region</th>
<th>Pathological lesions (Tuberculosis/Cryptococcosis)</th>
<th>Treatment Tuberculosis/Cryptococcosis</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/[3]</td>
<td>61/M</td>
<td>United States</td>
<td>Lung/ CSF</td>
<td>INH, SM/AMPH-B</td>
<td>Recovered</td>
</tr>
<tr>
<td>2/[4]</td>
<td>69/M</td>
<td>United States</td>
<td>Lung/ Lung</td>
<td>INH, REP/KCZ</td>
<td>Recovered</td>
</tr>
<tr>
<td>3/[5]</td>
<td>51/M</td>
<td>Spain</td>
<td>CSF/CSF</td>
<td>INH, REP, EB, PZA/AMPH-B, 5-FC</td>
<td>Recovered</td>
</tr>
<tr>
<td>4/[6]</td>
<td>34/F</td>
<td>Saudi Arabia</td>
<td>Lymph node / vertebra</td>
<td>INH,REP, EB, PZA/FLCZ</td>
<td>Recovered</td>
</tr>
<tr>
<td>5/[7]</td>
<td>24/F</td>
<td>Italy</td>
<td>CSF/CSF</td>
<td>INH, REP, EB, PZA, SM/FLCZ, L-AMB</td>
<td>Recovered</td>
</tr>
<tr>
<td>6/[8]</td>
<td>18/F</td>
<td>Canada</td>
<td>Lung/ CSF, Lymph node</td>
<td>INH, REP, EB, PZA/AMPH-B, S-FC, FLCZ</td>
<td>Recovered</td>
</tr>
<tr>
<td>7/[9]</td>
<td>65/M</td>
<td>India</td>
<td>Lung/ Lung</td>
<td>NA/AMPH-B</td>
<td>Recovered</td>
</tr>
<tr>
<td>8/[10]</td>
<td>58/F</td>
<td>Taiwan</td>
<td>Lymph node/ Lung</td>
<td>NA/FLCZ</td>
<td>Recovered</td>
</tr>
<tr>
<td>9/[11]</td>
<td>70/M</td>
<td>Iran</td>
<td>Lung/ CSF, Lung</td>
<td>INH, REP, EB, PZA/AMPH-B</td>
<td>Died</td>
</tr>
<tr>
<td>10/[12]</td>
<td>61/M</td>
<td>Rwanda</td>
<td>Lung, Bone marrow, Liver/ CSF</td>
<td>INH, REP, EB/AMPH-B, FLCZ</td>
<td>Recovered</td>
</tr>
<tr>
<td>11/ present case</td>
<td>84/F</td>
<td>Japan</td>
<td>Lung, Bone marrow, Liver, skin/ Lung</td>
<td>INH, REP, EB/FLCZ</td>
<td>Recovered</td>
</tr>
</tbody>
</table>

cases of co-infection with *C. neoformans* and *M. tuberculosis* as per table 2.

In the present case, it is impossible to know whether infection with tuberculosis preceded infection with Cryptococcus or vice versa. There is some evidence that both TB and Cryptococcus have immunomodulatory effects on host defenses. Three recent studies have explored the effects of TB on several different aspects of host immunity [14,15]. Two of them [14,15] used cells that were isolated from bronchoalveolar lavage fluid to study the expression of immune mediators in patients with TB. The third study [16] used induced sputum samples from TB patients, patients with other lung diseases and healthy controls to do the same. Collectively, the results of these studies suggest that the expression of immunosuppressive mediators inhibits host defenses against TB. The immunosuppressive mediators that have been identified as being upregulated in patients with active TB include both intracellular (e.g., suppressors of cytokine signaling, and that associated with interleukin receptor-associated) and extracellular (interleukin [IL]-10, transforming growth factor-beta RII, IL-1Rn, IDO, and CD163) molecules [14,15].

There is also evidence that *C. neoformans* can negatively affect the host immune system [17,18]. The main virulence factor of *C. neoformans* is an outer polysaccharide capsule that is composed primarily of glucuronoxylomannan (GXM) and galactoxylomannan (GalXM). GXM has been shown to have several effects on the host immune system, including inducing of suppressor T cells (which inhibit cell-mediated immunity), directly inhibiting T cell responses and inhibiting the movement of leukocytes into inflammatory sites [18]. A recent study demonstrated the ability of GXM to induce macrophage apoptosis in rats, both in *vivo* and *in vitro* [19]. This result was also documented in a study that used peritoneal macrophages to show that both GXM and GalXM can cause macrophage apoptosis [19].

References


