# Frequency of Pulmonary Fungal Infection in Egyptian Patients with Re-Treatment Pulmonary Tuberculosis and its Clinical and Radiological Significance

Takwa E. Meawed[1], Amany Fawzy M[2], Reda M El Gamry[2], Amany Shaker[2], Alaa El Gazzar[2] and Ahmad S. Ragheb[3]

[1]Microbiology & Immunology, [2]Chest and [3]Radiology Departments, Faculty of Medicine, Zagazig University, Egypt.
takwa_farid@hotmail.com

**Abstract: BACKGROUND**: Tuberculosis (TB) is the second most common Egyptian health problem after Schistsomiasis. Both TB and pulmonary fungal infections are chronic diseases of immunocompromised hosts. However, the co-association of both illnesses had not well-studied before in Egyptians. Treatment failure of TB, relapse and re-infection are major complications facing both physicians and microbiologists during follow up of tuberculous patients. **STUDY AIMS**: first, to spot light on the co-association of pulmonary fungal infection and re-treatment pulmonary TB patients, assess its frequency and its radiological findings. Second, to disclose the personal risk factors predisposing to this co-association. METHODS: a two-year prospective cross-sectional study included 258 TB outpatients, 26 were diagnosed as re-treatment pulmonary TB patients and investigated for association of fungal infection microbiologically, clinically and radiologically. Antimycobacterial drug susceptibility testing was done by MGIT 960. **RESULTS**: Most of re-treatment cases of TB were males in productive age. A statistical significant association between fungal isolation and MDR-TB, re-treatment tuberculous diabetic patients, old age and being a farmer with retreatment TB ($P$<0.05). Dyspnea and weight loss were the most frequent symptoms in these patients (100%). Histoplasma capsulatum was the most frequently isolated fungus from re-treatment TB cases (37.5%).The most frequent CT findings were bronchiectatic changes. **CONCLUSION**: Smear examination for fungi is recommended as a routine microbiology investigation for all re-treatment TB cases. Repeated sputum examination is highly recommended for diabetic TB patients, old age patient, farmers searching for retreatment and/or associated fungal infection. HRCT is recommended as low dose radiological modality assessing re-treatment TB cases.
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**Key Words:** Tuberculosis- fungi-Egypt- retreatment

## 1. Introduction

Tuberculosis remains a major public health problem worldwide. One-third of the world population is infected with Mycobacterium tuberculosis (1). According to WHO reports, TB is the second most important public health problem in Egypt, after *Schistosomiasis*. **WHO** estimates **(2010)**, Egypt is estimated to have 15000 TB cases and a rate of 18 cases per 100000 of population (2).Recurrence of active tuberculosis after treatment can be due to relapse of infection with the same strain or reinfection with a new strain of Mycobacterium tuberculosis. The proportion of recurrent tuberculosis cases caused by reinfection has varied widely in previous studies (3).

Despite the widespread distribution of the fungal spores in nature, it is difficult to predict the incidence of predisposition in patients (4). *Histoplasma capsulatum* is a slow-growing, dimorphic fungus that causes disease that ranges from focal and self-limited to disseminated, rapidly fatal in immunocompromised individuals, particularly those with lowered cell mediated immune response (5, 6).

The Global Plan to Stop TB (2006-2015) has been challenged by different causes including the problem of multidrug resistant TB (MDR TB) & extensively drug resistant TB (XDR) (7).

The aim of this study was firstly, to spot light on the co-association between pulmonary fungal infections and re-treatment pulmonary TB in Egyptian patients and to assess its frequency and different radiological findings with multi-detectors CT. Secondly we aimed to disclose the personal risk factors that predispose to this co-association.

## 2. Patients and Methods

This study was conducted out from April 2009 to March 2011 in Medical Microbiology and Immunology Department, Radiology & Chest Departments, Zagazig University, Hospitals and Zagazig Chest Hospital. The University Ethical Committee approved this study. Full consent was taken from all inpatients enrolled in this study before history taking or specimen collection.

### Study Design:

A prospective cross-sectional study included 258 tuberculous outpatients asked medical advice at TB outpatient clinics of both Zagazig University Hospitals & Chest Hospital, Zagazig, Sharkia Governorate,

Egypt, for initial clinical, radiological and microbiological assessment and treatment.
They were diagnosed as re-treatment pulmonary tuberculosis according to National TB Control Program of Egypt to (8) on the basis of:

1. History of receiving antituberculous drugs for more than one month.
2. Recurrence of general and / or local chest symptoms.
3. Documented positive Ziehl-Neelsen (ZN) smear or culture on LÖwenstein-Jensen (L J) media for acid fast bacilli AFB after reappearance of symptoms.

These re-treatment cases include patients with treatment failure, relapse and defaulters.
All the studied patients were subjected to:

(1) Thorough history taking stressing on general & local chest symptoms, history of DM, receiving corticosteroid therapy, associated autoimmune disorders & history of antituberculous drugs in the previous course.

(2) **Microbiology Specimen Processing:** Early morning spontaneously produced sputum specimens were taken from all of the study population for three successive days, if it was difficult, sputum induction by inhalation of nebulized 5 – 10 % hypertonic saline for 20 minutes (9). Rapid delivery of sputum specimens to the laboratory where the following was done.

a. Microscopic examination after Z-N staining searching for acid fast bacilli to ensure TB. Negative smears were repeated on the next two days.

b. Wet mounts with lactophenol cotton blue searching for hyphae or yeast cells.

c. **Fungal Culture Media and Growth Conditions:**

Cultivation on mycologic media including Sabouraud's dextrose agar (SDA: Oxoid) with chloramphenicol and cyclohexamide and brain-heart infusion blood agar (Oxoid) at room temperature and 37°C respectively. Macroscopic morphologic features of colonies were examined on both media every 24h, then microscopically evaluated. Temperature-induced mycelium-to-yeast conversion was done to proof culture of dimorphic fungal infection. Macroscopic examination of hyphae was done including growth rate, appearance and color. Direct microscopic examination for hyphae and conidia was done (10, 11).

d. Digestion-decontamination technique was done for the most purulent part of the specimen prior to culture on LÖwenstein-Jensen

e. Sputum culture on MGIT- 960 medium & performing antimycobacterial drug susceptibility testing for the standard first line drugs. This was done to define cases of MDR & XDR tuberculosis (this step was done in Central laboratories of Ministry of Health (MOH), where the results were collected from).

(3) Blood chemistry results:

a. Complete blood count (CBC)

b. Erythrocyte sedimentation rate ( ESR )

(4) Chest X-ray P-A & lateral views to be compared with the previous chest X-rays to detect new radiological data.

(5) Multidetector CT thoracic examination HRCT at MDCT GE healthcare with parameters include 100 to 120 kVp at 40 to 100 mAs, 1-1.5 mm collimation making ‘‘low-dose’’ thoracic CT more straight-forward reducing radiation exposure following the ALARA principle of ‘‘as low as reasonably achievable (12).

(6) Statistical analysis: All patients’ data were tabulated, processed using Statistical Package for Sciences and Society (SPSS 17.0) (SPSS Inc., Chicago, IL, USA). Qualitative variables were expressed by frequency and percentage and compared using chi-square test or Fischer’s exact test when appropriate

## 3. Results

Only 26 patients were fulfilling case definition of retreatment pulmonary TB out of 258 cases studied (10%). In history taking, these cases had interrupted or incomplete course of treatment during the 2 months duration following hospital discharge. They became smear positive for TB and went back to seek advice upon reappearance of symptoms after about 12 months or more of hospital discharge. All of them were males except two. However, Out of these 26 retreatment TB patients, 8 cases (30.8%) had combined pulmonary fungal and tuberculous infection on direct film by lactophenol cotton blue stain and culture on mycologic media. Their age was (35.5 ±13 years).

MDR TB, being a farmer, Diabetes mellitus and old age were significant risk factor ($P < 0.05$) regarding the isolation of fungi (Table 1).

Dyspnea and weight loss were the most frequent symptoms in patients with combined fungal infection and re-treatment TB (100%) each, followed by expectoration and hemoptysis (75%) each (Table 2).

The most frequently isolated fungal agent was *H. capsulatum* (37.5%) (Table 2). *H. capsulatum* culture from clinical specimens is sufficient for diagnosis, as it is not a common fungal contaminant. Colonies appeared at day 20 or 21 because it is a slow-growing fungus. Microscopic examination of culture was confirmatory to differentiate it from saprophytic molds by tuberculate macroconidia and by temperature-induced mycelium-to-yeast conversion.

Multi detectors HRCT findings of the studied patients revealed; The most frequent CT findings in patients with combined fungal and TB infection were bronchiectatic changes, followed by interstitial infiltrates then cavitations (75%, 50% and 37.5 %) respectively However, fungal ball, lobar fibrosis and mediastinal lymphadenopathy were the least frequent findings in (25%) only (Table 4).

Table 1: Percentage of risk factors among patients with combined re-treatment TB & fungal infection and patients with (re-treatment TB) only

| Risk factor | Combined re-treatment TB and fungal (8 patients) No. % | Re-treatment TB cases only (18 patients) No. % | (OR 95% CI) | *P* Value |
|---|---|---|---|---|
| Manual Worker 16 | 3 (18.75) | 13 (81.25) | 0.23 (0.03-1.78) | 0.18 |
| Farmer8 | 5 (62.5) | 3 (37.5) | 8.33 (1.0-93.6) | 0.03* |
| Not working 2 | 0 | 2 (100) | 0.0 (0.0-10.5) | 1.0 |
| History of dust exposure + 20 | 8 (40.0) | 12 (60.0) | Unidentified | 0.13 |
| - 6 | 0 | 6 (40.0) | | |
| Diabetes + 7 | 5 (71.5) | 2 (28.5) | 13.3 (1.27-193.3) | 0.01* |
| - 19 | 3 (15.7) | 16 (84.3) | | |
| Corticosteroid + 2 | 2 (100) | 0 | Unidentified | 0.08 |
| - 24 | 6 (25) | 18 (75) | | |
| Autoimmune disorders + 3 | 2 (66.7) | 1 (33.3) | 5.7 (0.3-195.3) | 0.21 |
| - 23 | 6 (26%) | 17 (74%) | | |
| Duration of clinical presentation | | | | |
| | 2 (28.6) | 5 (71.4) | 1.0 | 0.63 |
| ‹ 2y 7 | 3 (50) | 3 (50) | 2.5 (0.16-48.2) | 1.0 |
| 2-5 y 6 | 3 (23) | 10 (77) | 0.75 (0.06-9.5) | 0.67 |
| > 5 y 13 | | | | |
| Incomplete Course of + 22 | 7 (32) | 15 (68) | 1.4 (0.09-41.9) | 1.0 |
| antituberculous drugs - 4 | 1 (25) | 3 (75) | | |
| Smoking + 19 | 5 (26.3) | 14 (73.7) | 0.48 (0.05-4.04) | 0.63 |
| -7 | 3 (42.8) | 4 (57.2) | | |
| Male predisposition + 24 | 8 (33.3) | 16 (67.7) | Unidentified | 0.53 |
| | 0 | 2 (100) | | |
| Cavitations on initial radiograph + 17 | 7 (41) | 10 (59) | 5.6 (0.47-48.8) | 0.19 |
| - 9 | 1 (11.1) | 8 (88.9) | | |
| MDR organisms + 14 | 7 (50) | 7 (50) | 11 (1.0-2956) | 0.03* |
| - 12 | 1 (8.4) | 11 (91.6) | | |
| Old age at diagnosis + 6 | 5 (83.3) | 1 (16.7) | 28.3 (1.84-956) | 0.004 |
| - 20 | 3 (15) | 17 (85) | | |
| Initial body weight below 50 Kg +9 | 5 (55.5) | 4 (45.5) | 5.83 (0.72-56.0) | 0.07 |
| -17 | 3 (17.7) | 14 (82.3) | | |
| Infected contact with TB in the same +3 | 2 (66.7) | 1 (33.3) | 5.67 (0.3-195.3) | 0.21 |
| Locality - 23 | 6 (26) | 17 (73.9) | | |

Table 2: Clinical presentations of patients with combined re-treatment TB and fungal infection & those with re-treatment TB only

| Clinical presentation | Combined re-treatment TB and fungal infection No.=8 | Re-treatment TB cases only No.=18 | *P*- Value |
|---|---|---|---|
| Fever | 2 | 10 | 0.21 |
| Weight loss | 8 | 12 | 0.13 |
| Cough | 2 | 12 | 0.08 |
| Expectoration | 6 | 16 | 0.56 |
| Hemoptysis | 6 | 4 | 0.02* |
| Dyspnea | 8 | 14 | 0.27 |
| Chest wheeze | 2 | 8 | 0.41 |

Table 3: Isolated organisms from combined cases of re-treatment TB and fungal infection (Total cases = 8):

| Isolated fungus | No. | % |
|---|---|---|
| *H. capsulatum* | 3 | 37.5 |
| *A.niger* | 2 | 25 |
| *Candida albicans* | 1 | 12.5 |
| *Fusariumsolani* | 1 | 12.5 |
| *Candida parapsillosis* | 1 | 12.5 |

Table ( 4 ):Radiological presentation (Multidetector CT) in patients with combined re-treatment pulmonary tuberculosis and fungal infection & those with re-treatment pulmonary tuberculosis only.

| MDCT findings | Combined relapsed TB & fungal infection No. = 8 | Relapsed TB No. = 18 | *P* - value |
|---|---|---|---|
| Cavitations | 3 | 12 | 0.21 |
| Fungus ball in a cavity | 2 | 0 | 0.087 |
| Bronchiectatic changes | 6 | 3 | 0.007** |
| Segmental or labor fibrosis | 2 | 12 | 0.08 |
| Interstial infiltrates | 4 | 0 | 0.004** |
| Centrilobular nodules | 2 | 8 | 0.41 |
| Mediastinal lymphadenopathy | 2 | 0 | 0.08 |

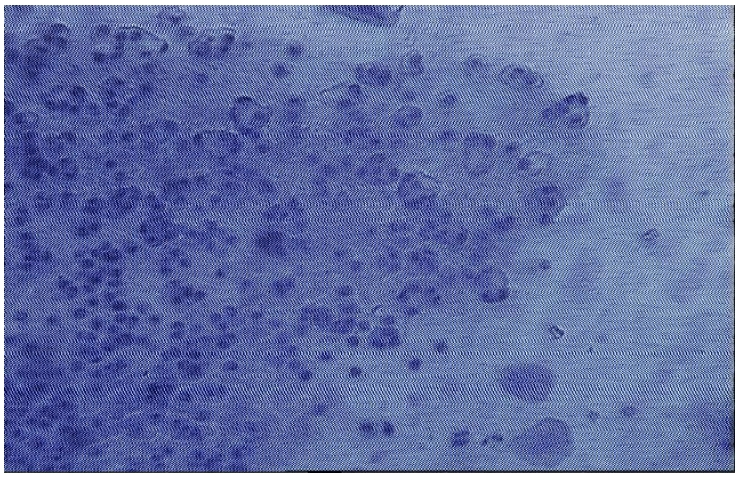

**Fig. (1):** Wet film with lactophenol cotton blue showing numerous small narrow-base budding yeast cells (1-5um) inside macrophages of *H. capsulatum var. capsulatum*

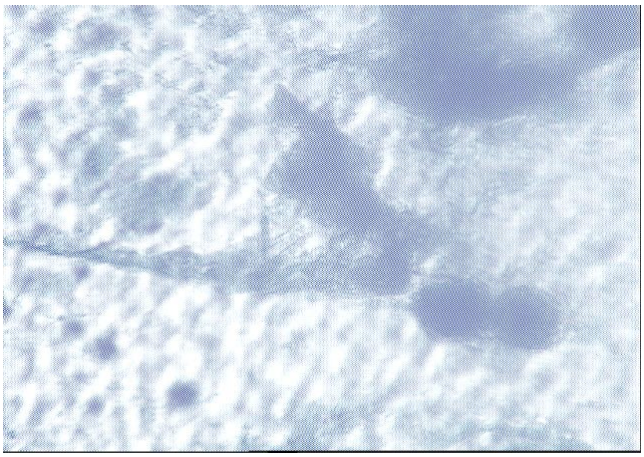

**Fig. (2):** Lactophenol cotton blue staining showing large, rounded, tuberculate, single-celled macroconidia of *Histoplasma capsulatum***.**

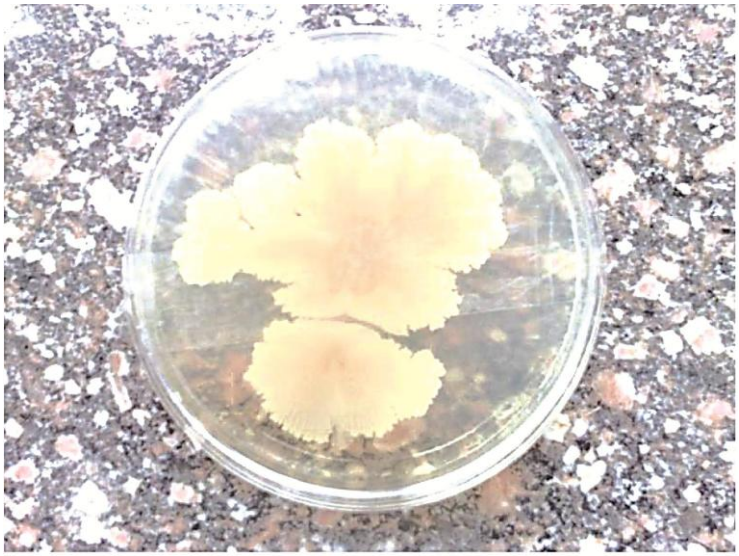

**Fig. (3):** Brain-heart infusion agar showing lobulated colonies of subculture of *Histoplasma capsulatum.*

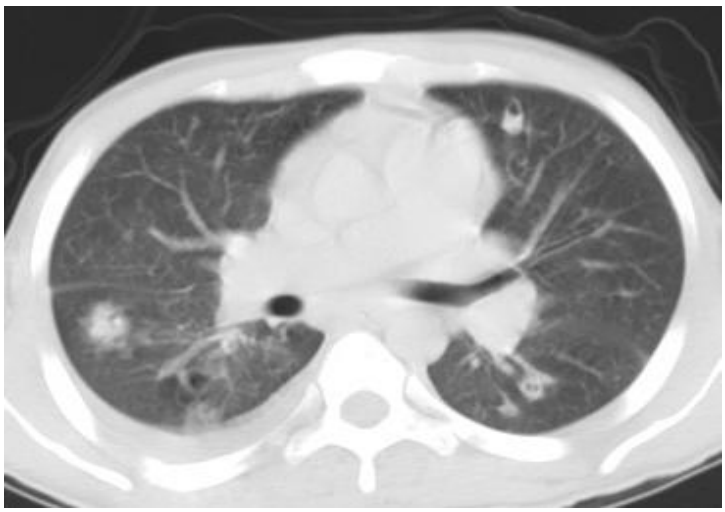

**Fig. (4):** HRCT of relapsed T.B with superadded small nodular fungal infection some of these small nodules showing cavitation.

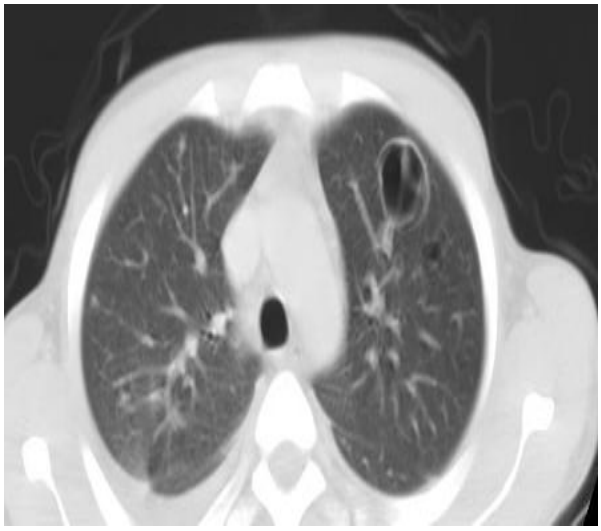

**Fig. (5):** HRCT shows myceytoma at left upper lobe with crescent of air and right apical fibrotic strands.

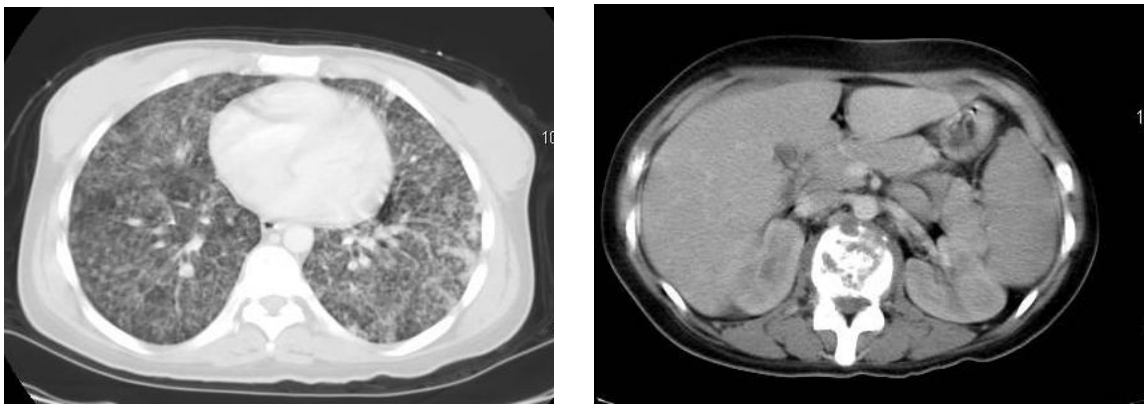

**Fig. 6 (a & b): HRCT** lower cuts of relapsed patient show extensive miliary nodular and fine reticular infiltrates as well as spondylodiscitis at dorso-lumbar region.

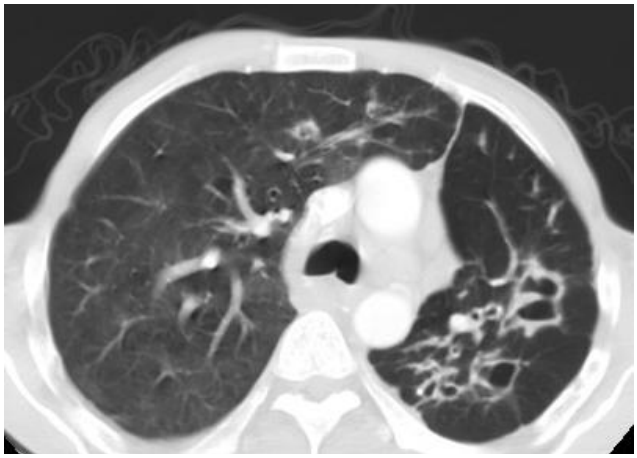

**Fig. (7):** HRCT of relapsed patient with combined cystic and traction bronchiectasis.

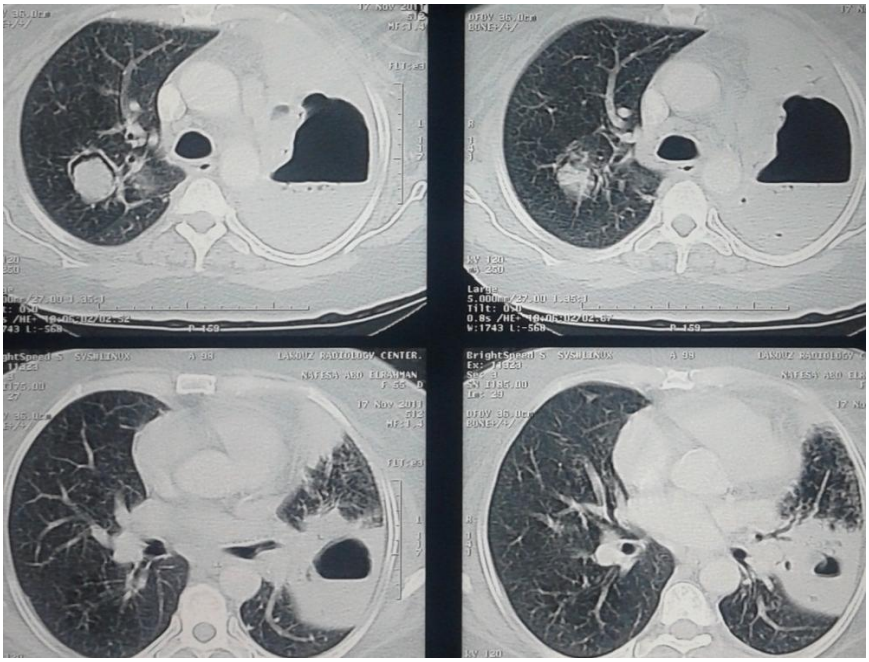

**Fig. (8):** Complicated T.B with right apico-posterior fungus ball and left sided cavitary lesion with air fluid level

**4. Discussion**

All Egyptian tuberculous patients with AFB smear-positive sputum were admitted to Chest Hospitals, TB Departments at least for two months to receive regimen I course of treatment and close medical and general observation, and then followed up for another four months twice weekly in TB outpatient clinic to complete regimen I course. Afterward, most of them convert into smear and culture negative for TB within two weeks. However, for bad luck, some cases recur again to the clinic seeking medical advice and return back to have smear +ve AFB on follow up visits.

In the present work, being a farmer and old age were significant risk factors for concomitant fungal and TB infections that issue was discussed before by Wang et al about a 62-year-old poultry farmer from the island of Java, Indonesia, diagnosed with disseminated histoplasmosis (13). Prevalence of co-association between retreatment pulmonary TB and pulmonary fungal infection presented 30.8% in this study with no previous data to compare with in our locality.

WHO Regional Office in Cairo estimates that (17%) of TB cases in the eastern Mediterranean are attributable to smoking of water pipes, this study revealed that smoking was represented in (62.5%) of retreatment TB cases with concomitant fungal infection (14).

This study was unique in scope in this locality as it dealt with concomitant fungal infection in retreatment Egyptian TB cases, however, there was a case report reported by **Jeong *et al.*, (15)** showed agreement with our results regarding this co association discussing a Korean male lived 5 years in Guatemala, returned back to his country, diagnosed with (AIDS) with disseminated tuberculosis then treated with anti-tuberculosis and anti-retroviral agents. However, despite treatment Fever, weakness, hepatosplenomegaly and pancytopenia were persistent. The patient's history of living in Guatemala directed the authors to search for other opportunistic infections where bone marrow aspiration and biopsy were performed and the result revealed numerous intracellular organisms consistent with *Histoplasma capsulatum*; therefore, the diagnosis of disseminated histoplasmosis was made but unfortunately it was postmortem. The positive findings between our study and that of **Jeong *et al.*, (15)** firstly is in Guatemala, TB has become a serious public health problem; according to **WHO, 2010**, the current rate of new TB cases is estimated to be 3170 cases / 100,000 inhabitants (16). The second point is that people in Guatemala have risk factors for susceptibility to fungal infection like AIDS, while in our locality, retreated TB cases, DM, other chronic medical conditions are favoring conditions in acquiring histoplasmosis. The last one is Guatemala has a mean average humidity of 65.1% and up to 72% in summer months near to the average humidity in Egypt.

However, in contrast to ours, Guatemala has a high endemicity of histoplasmosis as one of central American countries.

**Wheat *et al.*** (17) illustrated that chronic pulmonary histoplasmosis occurs in patients with underlying lung disease and is characterized by

persistent or recurrent pulmonary symptoms, progressive lung infiltrates, fibrosis & cavitation.

About *Fusarium solani*, it was isolated from only one (12.5%) of retreatment TB cases with fungal infection; an immunocompromised patient with history of Schistosomiasis 14 years ago with advanced liver cirrhosis and hypersplenism. However, researchers in mycology fields (18,19) recovered *Fusarium solani* from immunocompromised patients other than retreatment TB, as being an emerging and life-threatening fungal infection during these decades. *Fusarium* infection has a worse outcome, limited therapeutic options and more resistance than the more common *Aspergillus* infection.

The association of diabetes mellitus and TB had been studied many years ago and regardless of study design it can be summarized according to (20,21)as diabetic patients have increased incidence, more advanced forms of tuberculosis, higher mortality rates and poor outcome than non-diabetics due to cellular immunodeficiency including decreased cytokine levels, T- and NK cells, reduced CD3 and CD56 surface markers, reduced complement receptor 3 (CR3) expression on monocytes surface, reduced IL2 receptors on lymphocytes.

In the present study *Aspergillus Niger* was isolated from the sputua of two tuberculous patients. Radiologic examination of those patients revealed fungal ball in a pre-existing TB cavity. Other researchers (22, 23) illustrated that infection with *Aspergillus* species causes a wide spectrum of human illnesses depending on host immune status ranges from simple colonization in normal host up to aspergilloma or invasive aspergillosis. That was proved by **Vaideeswar *et al.*,** that bronchial damage and cavitatory/ cystic parenchymal disease predisposes to aspergilloma in some TB patients (24)

Multidrug and extensively drug-resistant TB **WHO** Global report 2012 (25) comprised 35 countries including Egypt on Surveillance and response. It was estimated that 4,040,000 cases of MDR-TB emerged globally in 2008 and causing an estimated 1,050,000 deaths. There is a clear need for strengthening case holding and treatment monitoring.

**Prasad 2010** recommended proper use of second-line drugs must be ensured to cure existing MDR-TB, reduce its transmission and to prevent XDR-TB. Sound infection control measures to avoid further transmission of M/XDR-TB and research towards development of new diagnostics, drugs and vaccines should be promoted to control M/XDR-TB (26).

The results of radiographs confirmed by HRCT enabled easy and rapid examination of the patients with different pulmonary disease as those patient always complain of breath shortness so cannot withstand long examination time. HRCT enabled examination of the whole lungs in a single breath hold, the immune compromised T.B patients with suspicion of super added fungus infection need low dose radiation that can be achieved by HRCT, protecting the patient from unnecessary radiation exposure (27).

Misdiagnosis of cases as being only pulmonary tuberculosis and not combined tuberculous and fungal infection leads to waste of time and money searching for the lost dream that the patient is completely free from original symptoms while he/she is still infected with another enemy called concomitant fungal infection. Primitive methods used in diagnosis lead to restriction of knowledge and bad judgments of the case resulting in handicapping of both physician and microbiologist during decision making while waiting for acid-fast negative smear.

**Conclusions and Recommendations**

Prevalence of concomitant retreatment TB and fungal infection was (30.8%). There was statistical significant association between MDR-TB, retreatment tuberculous diabetic patients, old age and farmers with pulmonary fungal infection ($P$<0.05). Retreatment TB patients with autoimmune disorders, underweight, those with infected TB family contact and those with lung cavitations on X-ray films had more than 5 times risk than retreatment TB patients without previous risks. *Histoplasma capsulatum* was the most frequently isolated fungus from retreatment TB cases (37.5%). Smear examination for fungi is highly recommended to be done as a routine microbiology laboratory investigation for all cases with retreatment TB. Sputum examination for fungi and AFB should be done for all diabetic patients with chest complaints. Cases with MDR TB should be regularly examined for relapse and associated fungal infection. In addition to tuberculosis, physicians need to be aware of histoplasmosis as a possible infection in immunocompromised patients as disseminated histoplasmosis and tuberculosis have similar clinical manifestations. This study may direct attention of future researchers in this field to be minded to a new distribution of fungi. HRCT with short examination time and low dose of radiation is a suitable imaging modality tool and can accurately detect cavitations, fungus ball, reticulo-nodular infiltrates, bronchiectatic changes and even lymphadeopathy.

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**Corresponding author:**

Takwa E. Meawed

Microbiology & Immunology Department, Faculty of Medicine, Zagazig University, Egypt

takwa_farid@hotmail.com

**References**


1. Van Crevel, R. Tom H. M. Ottenhoff, and Jos W. M. van der Meer (2002): Innate Immunity to Mycobacterium tuberculosis. Clinical Microbiology Reviews, 15, 2: 294-309
2. WHO Report (2010): WHO estimates of TB incidence by country available at: http://www.who.int/tb/country/data/download/en/ index.html
3. Bassili A, Grant AD, El-Mohgazy E, Galal A, Glaziou P, Seita A, Abubakar I, Bierrenbach AL,Crofts JP. van Hest NA (2010):. Estimating tuberculosis case detection rate in resource-limited countries: a capture-recapture study in Egypt. Int J Tuberc Lung Dis. 14 (6):727-32.
4. Shah R, Vaideeswar P, Pandit SP (2008): Pathology of pulmonary aspergillomas - Indian J Pathol Microbiol., :51(3 ) : 342-345
5. Rippon, J. W. (1988): Histoplasmosis, In J. W. Rippon (ed.), Medical mycology p. 381-423. The W. B. Saunders Co., Philadelphia, Pa.
6. Wheat, L. J., G. Sarosi, D. McKinsey, and R. Hamill (2000): Practice guidelines for the management of patients with histoplasmosis. Clin. Infect. Dis., 30:688-695.
7. WHO (2012): Guidelines for treatment of tuberculosis; 4thed (Stop TB Strategy) available at http://www.who.int/tb/features_archive/global_plan_to_stop_tb/en/
8. National Tuberculosis Control Program of Egypt (2008): Guidelines on management of tuberculosis, Egypt. Ministry Of Health & Population; page:13
9. Pin I, Gibson PG & Kolendowicz (1992): Use of induced sputum cell count to investigate airway inflammation in asthma. Thorax; 47:25-29.
10. Forbes, B, Sahm, DF and Weissfeld, A Baily and Scott (2007): Diagnostic Microbiology Chicago, El Sevier 12th Ed. Ch 53: Infections of the Lower Respiratory Tract.
11. Koneman, EW, Allen, SD, Janda, WM, Schreckenber, PC and Winn, WC (2005): Color Atlas and Text Book of Diagnostic Microbiology, 6th Ed, Philadelphia Lippincott William & Wilkins, Mycology, 989-994
12. Yanagawa M, Tomiyama N, Honda O, Kikuyama A, Sumikawa H, Inoue A, Tobino K, Koyama M, Kudo M. (2010):Multidetector CT of the lung: image quality with garnet-based detectors. Radiolog.; 255 (3): 944-54.
13. Wang' T. L., Cheah J. S and Holmberg K (1996): Case report and review of disseminated histoplasmosis in South-East Asia: clinical and epidemiological implications Tropical Medicine and International., 1: 35-42
14. WHO (2008): Regional Office in Cairo EGYPT: Water pipe smoking a significant TB risk. March 2008 at IRIN humanitarian news and analysis
15. Jeong, H, Sohn, J, Kim, M, Choi, J, Kim, C, Choi, S, Kim, J and Cho Y (2007): Disseminated Histoplasmosis and Tuberculosis in a Patient with HIV Infection. Yonsei Med J 30;48 (3):531-534.
16. WHO report (2010): Tuberculosis profile: (Guatemala) Error! Hyperlink reference not valid.
17. Wheat LG, Goldman M and Knox K (2008): Cryptococcosis and the endemic mycosis. Chapter (132). In Fishman's Pulmonary Diseases and Disorders. 4th Edition. Editor: Fishman AP, Elias JA, Fishman JA, Grippi M, Senior R & Pack A. Mc Grow Hill company. Page 2329-2349. Volume II.
18. Marom, M. Holmes A, Bruzzi1, J Truong M O'Sullivan J. and Kontoyiannis D (2008): Imaging of Pulmonary Fusariosis in Patients with Hematologic Malignancies AJR; 190:1605-1609.
19. Selleslag D (2006): A case of fusariosis in an immunocompromised patient successfully treated with liposomal amphotericin B Acta Biomed 77 S 2:32-35
20. Jeon, C and. Murray M. (2008): Diabetes Mellitus Increases the Risk of Active Tuberculosis: A Systematic Review of 13 Observational Studies. PLoS Medicine; 5 (7): e152
21. Baker MA, Harries AD, Jeon CY, Hart JE, Kapur A, Lönnroth K, Ottmani SE, Goonesekera SD, Murray MB (2011): The impact of diabetes on tuberculosis treatment outcomes: a systematic review. BMC Med. ;9:81
22. Georgios C & Kontonyianis DP (2008): Aspergillus, Candida & other opportunistic mold infection of the lung, Chapter 131, In Fishman's Pulmonary Diseases and Disorders. 4th edition. Editor: Fishman AP, Elias JA, Fishman JA, Grippi M, Senior R & Pack A. Mc Grow Hill company. Volume II, P 2292-2325..
23. Stevens, D.A.; Kan, V.L.; Judson, M.A. *et al*. (2000): Practice guidelines for diseases caused by Aspergillus. Clin. Infect. Dis., 30: 696-709.
24. Vaideeswar P, Prasad S, Deshpande JR, Pandit SP. (2004): Invasive pulmonary aspergillosis: A study of 39 cases at autopsy. J Postgrad Med.; 50:21-6.
25. WHO Report (2012): MDR & XDR TB. At www.who/tb/challenges/mdr/en/
26. Prasad R. (2010): Multidrug and extensively drug-resistant TB (M/XDR-TB): problems and solutions. Indian J Tuberc; 57(4): 180-91.
27. Bushong, S.C., (2001): Radiologic Science for Technologist: Physics, Biology, and Protection, 7th ed., St. Louis, Missouri: Mosby, Inc.