INTRODUCTION

Tuberculosis (TB) is an infectious bacterial disease caused by Mycobacterium tuberculosis, which most commonly affects the lungs and it is usually spread from person-to-person through the air by droplet nuclei that are produced when a person with pulmonary or laryngeal tuberculosis coughs or sneezes ***(Egyptian TB Guidelines, 2017).***

Worldwide, TB is one of the top 10 causes of death and millions of people continue to fall sick with TB each year ***(Global Tuberculosis Report, 2019).***

Despite intense investment from both governmental and private sectors, tuberculosis (TB) continues to cause substantial morbidity and mortality in several countries worldwide. A major concern in TB control is the emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB in various endemic regions ***(WHO, 2018).***

The emergence of multidrug-resistant tuberculosis (MDR-TB) is bringing new challenges. MDR-TB is caused by Mycobacterium tuberculosis (M. tuberculosis) that is resistant to isoniazid and rifampicin, with or without resistance to other anti-tuberculosis drugs ***(Santin, 2016).***

Drug-resistant TB continues to be a public health crisis. The best estimate is that, worldwide in 2017, 558 000 people developed TB that was resistant to rifampicin (RR-TB), the most effective first line drug, and of these, 82% had multidrug-resistant TB (MDR-TB) ***(World Health Organization, 2018).***

In places where there is emergence of drug resistance, TB eradication becomes difficult and the mortality rates documented at 24 and 60 months from diagnosis in these regions are 46% and 73% of patients, respectively ***(Petersen and Chen, 2015).***

Clinical trials that evaluate new anti-tubercular drugs and treatment regimens take years to complete due to the slow clearance of Mycobacterium tuberculosis infection and the lack of early biomarkers that predict treatment outcome ***(Walzl et al., 2014; Clifford et al., 2015).***

There are no well-established host-derived biomarkers that are reliable surrogate markers of successful treatment in large prospective studies. A better understanding of the utility of immune and inflammatory markers as readouts of treatment outcomes can potentially lead to development of innovative prediction tools as well as to establishing targets for host-directed therapies to optimize treatment efficacy ***(Miranda et al., 2017).***

C-reactive protein (CRP) is a protein found in the blood and is used mainly as a marker of inflammation and infection, measuring and charting CRP values can prove useful in determining the progress of TB and the efficacy of the anti-tubercular treatment ***(Lawn et al., 2017).***

Erythrocyte sedimentation rate is a simple, cheap and commonly used test which has been in use since the early twentieth century. It is sensitive to inflammation ***(Wolfe and Pincus, 2001).***

Serum ESR and CRP can be used easily as a biomarker for monitoring of MDR-TB as their levels were significantly higher in TB patients than in healthy controls, and were higher in MDR-TB patients than in DS-TB patients **(Kilicarslan et al., 2013 and Lawn et al., 2017**).

Aim of the Work

This study aimed to test whether erythrocyte sedimentation rate and circulating levels of CRP accurately reflect mycobacterial loads and inflammation in MDR -TB patients and which one of them is more sensitive in this aspect.

Chapter (1): Pulmonary Tuberculosis

Definition:

Tuberculosis is an infectious disease caused by the bacillus Mycobacterium tuberculosis. It typically affects the lungs (pulmonary TB), but can also affect other sites (extrapulmonary TB). The disease is spread when people who are sick with pulmonary TB expel bacteria into the air, for example by coughing ***(WHO, 2018).***

Historical aspects of tuberculosis:

Tuberculosis (TB) has a long history. It was present before the beginning of recorded history and has left its mark on human creativity, music, art, and literature; and has influenced the advance of biomedical sciences and healthcare. Its causative agent, Mycobacterium tuberculosis, may have killed more persons than any other microbial pathogen ***(Daniel, 2006).***

TB was documented in Egypt, India, and China as early as 5000, 3300, and 2300 years ago, respectively ***(Daniel, 2006).***

Mycobacterium tuberculosis was discovered in 1882 by Robert Koch, He isolated and cultured M. tuberculosis from crushed tubercles. His experimental work identified the bacterium as the TB etiological agent ***(Daniel, 2006).***

The tuberculin skin test became the principal tool for infection diagnosis. In the same period, Koch developed staining methods for the identification of the bacillus; these techniques were subsequently improved by the German Doctor and bacteriologist Paul Ehrlich, whose method for detection of the bacillus provided the basis for the development of the Ziehl-Nielsen staining, which still is an important tool to diagnose TB ***(Ducati et al., 2006).***

In 1900, Calmette and Guerin discover the vaccine (BCG) that was obtained from attenuation of a strain of Mycobacterium bovis ***(WHO, 2018).***

Streptomycin (1943), P- amino salicylic acid (1949), Izonaizid (1952), Pyrazinamide (1954), cycloserine (1955), Ethambutol (1962) and Rifampicin (1963) were introduced as anti-TB agents, leading to progressive decline in TB incidence in the industrialized countries ***(WHO, 2018).***

Epidemiology of TB:

The burden of TB is highest in Asia and Africa. The African region has 24% of the world's cases.

Tuberculosis remains a major global health problem, responsible for ill health among millions of people each year. TB ranks as the second leading cause of death from an infectious disease worldwide after the human immunodeficiency virus (HIV) ***(WHO, 2018).***

In 2017, 10.0 million people developed TB disease 5.8 million men, 3.2 million women and 1.0 million children and TB caused an estimated 1.3 million deathsamong HIV-negative people and there were an additional 300 000 deaths from TB among HIV-positive people ***(WHO, 2018).***

In Egypt and According to the latest WHO estimation, the incidence is 15 cases per 100,000 populations in the year 2015 ***(Egyptian TB Guidelines, 2017).***

Causative organism

Tuberculosis is caused by any one of three mycobacterial pathogens: M. tuberculosis, Mycobacterium bovis, and Mycobacterium Africanum. Because M. bovis and M. Africanum produce relatively few cases of human tuberculosis, they are not considered separately ***(Riley et al., 2013).***

Mode of transmission

Person-to-person transmission of TB occurs via inhalation of droplet nuclei (airborne particles 1 to 5 microns in diameter). Coughing and singing facilitate formation of droplet nuclei. Persons with active untreated respiratory tract disease (pulmonary or laryngeal) are

contagious, particularly when cavitary disease is present or when the sputum is AFB smear positive. However, patients with sputum smear-negative, culture-positive pulmonary TB can transmit infection. Extra-pulmonary disease also has pulmonary disease; such individuals are contagious ***(Sepkowitz, 1996).***

Risk factors for TB:

There are a number of risk factors for tuberculosis infection; worldwide the most important of these is HIV. Co-infection with HIV is a particular problem in Sub-Saharan Africa, due to the high incidence of HIV in these countries ***(Chaisson, 2008).***

HIV infection increases the risk of tuberculosis by 20-40 folds, and tuberculosis accounts for 25% of HIV-related deaths worldwide ***(WHO report, 2018).***

Smoking more than 20 cigarettes a day increases the risk of TB by two to four times ***(Davies et al., 2006),*** while silicosis increases the risk about 30 fold ***(ATS/CDC, MMWR, 2000).***

Diabetes mellitus is also an important risk factor that is growing in importance in developing countries ***(Restrepo, 2007).***

Other disease states that increase the risk of developing tuberculosis are Hodgkin lymphoma, end stage renal disease, chronic lung disease, malnutrition, and alcoholism ***(Kumar et al., 2007).***

A person's genetics also plays a role ***(Möller et al., 2010).***

Pathogenesis

About 90% of those infected with M.tuberculosis have asymptomatic, latent TB infections (sometimes called LTBI) ***(Skolnik, 2011).***

TB infection begins when the Mycobacteria reach the pulmonary alveoli, where they invade and replicate within endosomes of alveolar macrophages ***(Kumar et al., 2007; Houben et al., 2006).*** The primary site of infection in the lungs, known as the "Ghon focus", is generally located in either the upper part of the lower lobe, or the lower part of the upper lobe ***(Kumar et al., 2007).*** Tuberculosis of the lungs may also occur via infection from the blood stream. This is known as a Simon focus and is typically found in the top of the lung ***(Khan, 2011).*** This hematogenous transmission can also spread infection to more distant sites, such as peripheral lymph nodes, the kidneys, the brain, and the bones ***(Herrmann, 2005; Kumar et al., 2007).***

All parts of the body can be affected by the disease, though for unknown reasons it rarely affects the heart, skeletal muscles, pancreas, or thyroid ***(Agarwal et al., 2005).***

If TB bacteria gain entry to the bloodstream from an area of damaged tissue, they can spread throughout the body and set up many foci of infection, all appearing as tiny, white tubercles in the tissues ***(Crowley, 2010).*** This severe form of TB disease, most common in young children and those with HIV, is called miliary tuberculosis ***(Anthony, 2005).*** People with this disseminated TB have a high fatality rate even with treatment (about 30%) ***(Ghosh et al., 2008; Jacob et al., 2009).***

Definitions of tuberculous cases

Case of tuberculosis

A patient, in whom tuberculosis has been confirmed bacteriological or diagnosed by a clinician.

Definite case

A patient with positive culture for the M. tuberculosis complex. In countries where culture is not routinely available, a patient with two sputum smears positive for acid-fast bacilli is also considered a definite case.

Pulmonary case

A patient with tuberculosis disease involving the lung parenchyma.

Smear-positive pulmonary case

A patient with at least two initial sputum smears positive for AFB (acid-fast bacilli); or one sputum examination positive for AFB and radiographic abnormalities consistent with active pulmonary tuberculosis as determined by a clinician; or one sputum specimen positive for AFB and culture positive for M. tuberculosis.

New case

A patient who has never had treatment for tuberculosis or who has taken anti-tuberculosis drugs for less than one month.

Relapse case

A patient previously declared cured but with a new episode of bacteriologically positive (sputum smear or culture) for AFB (acid-fast bacilli).

Re-treatment case

A patient previously treated for TB, who is started on a re-treatment regimen after previous treatment has failed

(treatment after failure), who returns to treatment having previously defaulted, or who was previously declared cured or treatment completed and is diagnosed with bacteriologically positive (sputum smear or culture) TB (relapse) ***(WHO, 2018).***

Definitions of treatment outcomes

Cured

A patient who was initially smear-positive and who was smear-negative in the last month of treatment and on at least one previous occasion.

Completed treatment

A patient who completed treatment but did not meet the criteria for cure or failure. This definition applies to pulmonary smear-positive and smear-negative patients and to patients with extra pulmonary disease.

Died

A patient who died from any cause during treatment.

Failed

A patient who was initially smear-positive and who remained smear-positive at month 5 or later during treatment.

Defaulted

A patient whose treatment was interrupted for 2 consecutive months or more.

Transferred out

A patient who transferred to another reporting unit and for whom the treatment outcome is not known.

Successfully treated

A patient who was cured or who completed treatment ***(WHO, 2018).***

Diagnosis of Pulmonary TB

A) Clinical Presentation of Pulmonary TB

1. **Symptoms**

The main symptoms of pulmonary tuberculosis are:

- Persistent cough of 2 weeks or more or any duration if HIV positive with or without Production of sputum which may be blood-stained not responding to non-specific treatment (including antibiotics with no anti-TB effect i.e. avoid Rifampicin, aminoglycosides and Quinolones).
- Fever for more than 2 weeks mainly at night.

- Night sweats.
- Breathlessness.
- Chest pain.
- Loss of appetite and loss of weight.
- History of contact sometimes could be detected.

(Egyptian TB Guidelines, 2017).

2. Physical signs

- Physical signs are non-specific and may not be helpful in confirming the diagnosis
- Chest - there may be crackles in the lung apices more pronounced on deep breathing; localized wheeze in local obstruction or pressure; dullness where there is effusion and in chronic disease there may be extensive fibrosis with the trachea pulled to one side ***(Egyptian TB Guidelines, 2017).***

B) Bacteriological diagnosis

Bacteriological diagnosis of TB still relies on detection of acid fast bacilli on microscopic examination and on culture; routine diagnostic methods that are very similar to those used 100 years ago ***(Grant et al., 2008).***

Every pulmonary TB presumptive should submit three sputum samples (at least two samples) and sputum Smear stained by (Z-N stain) for microscopy ***(Egyptian TB Guidelines, 2017).***

In cases where there is no spontaneous sputum production, a sample can be induced, usually by nebulized inhalation of a saline or saline with bronchodilator solution. A comparative study found that inducing three sputum samples is more sensitive than three gastric washings ***(Brown et al., 2007).***

When the patient presents with symptoms consistent with tuberculosis and dealt with as a presumptive case, then all the received sputum smears results are negative we should do sputum examination by GeneXpert ***(Egyptian TB Guidelines, 2017).***

The only rapid test for diagnosis of TB currently recommended by WHO is the Xpert® MTB/RIF assay

It can provide results within 2 hours, and was initially recommended (in 2010) for diagnosis of pulmonary TB in adults. Since 2013, it has also been recommended for use in children and to diagnose specific forms of extrapulmonary TB. The test has much better accuracy than sputum smear microscopy ***(WHO report, 2018).***