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Original Article

Mycobacterium tuberculosis infection in systemic lupus erythematosus patients

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ABSTRACT

Aim of the work: To estimate prevalence of tuberculosis (TB) infection in systemic lupus erythematosus (SLE) patients; to study its relation to disease duration, activity, damage and treatment as well as to compare the performance of interferon gamma (IFN-γ) release assay and tuberculin skin test (TST) in detection of TB infection.

Patients and methods: The study enrolled 100 adult SLE patients. Disease activity was assessed using the British Isles Lupus Assessment Group (BILAG) activity index and damage using the Systemic Lupus International Collaborative Clinics damage Index (SLICCDI). Tuberculin skin tests and QuantiFERON-TB GOLD In-Tube (QFT-GIT) test were performed.

Results: The mean age of the patients was 29.82 ± 7.9 years; 90% females and 10% males with a mean disease duration 5.5 ± 5.4 years. The BILAG index showing that 30% had category A renal activity and the mean of SLICCDI was 1.4 ± 1.7. All patients were Bacille Calmette-Guérin (BCG) vaccinated; none of them had a previous history or contact to members with TB infection. QFT-GIT was positive in 13 patients and TST was positive in 2 patients. 15 patients were diagnosed as latent tuberculosis infection (LTBI). No patients were identified with active TB and microscopic examination and culture were negative. The agreement between the QFT-GIT and TST was poor. No significant difference between patients with positive and negative QFT-GIT results as regard disease duration, corticosteroids and immunosuppressive drugs used, BILAG, SLICCDI, chest X-ray and laboratory investigations.

Conclusion: The prevalence of LTBI in SLE patients in our study was 15% with poor agreement between the QFT-GIT and TST.

1. Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disorder characterized by microvascular inflammation with the generation of autoantibodies. The cause of SLE is unknown, however, multiple factors are associated with its development, including genetic, racial, hormonal and environmental [1,2]. Infections are among the most important causes of morbidity and mortality in SLE patients [3]. SLE has been associated with increased risk of tuberculosis (TB) and SLE patients should be considered as a high-risk group for TB and active screening for latent patients and treatment for positive TB cases is needed [4].

Tuberculosis has existed for millennia and remains a major global health problem. It causes ill-health in a large number of people every year and in 2016 was one of the main 10 reasons for death around the world [5]. Around 90% of those infected with *Mycobacterium tuberculosis* are asymptomatic, sometimes called latent TB infection (LTBI), with only a 10% lifetime chance that a latent infection will advance to TB disease [6]. Immunosuppressed subjects are one of the most important targets for the screening of LTBI because of the high risk of progression to active TB [7]. Tuberculin skin tests (TSTs) have been utilized worldwide for over a century as a guide in diagnosing both LTBI and active tuberculosis. A positive TST result is associated with an increased risk for current or future active tuberculosis. However, certain limitations are associated with its use [8]. Many tuberculosis diagnostic techniques are being used in clinical practice, however their role in the various risk groups is yet to be determined. They are based on the detection of gamma interferon in the blood (IFN-γ release assay), which is

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released in response to in vitro stimulation of primed T-cells with particular antigens of *Mycobacterium tuberculosis* [9].

A high rate of TB has been reported in SLE patients, with an increased occurrence of extra-pulmonary forms and high mortality rates, particularly in developing countries, where TB is endemic [10]. In SLE patients, tuberculosis infection flourishes under conditions of immunosuppression which may either be secondary to the disease itself or to its treatment [11]. Despite the importance of the detection and treatment of LTBI to control TB in developing countries, especially in immunosuppressed patients, the frequency of TB or LTBI in SLE patients living in Egypt has not been reported yet. Also, no studies have evaluated the performance of IFN-γ release assays in detection of *Mycobacterium tuberculosis* infection in those patients. For this reason, we conducted the current study.

The aim of this study was to estimate the prevalence of *Mycobacterium tuberculosis* infection in adult SLE patients and to study its relation to disease duration, activity, damage and treatment. Also, to compare the performance of IFN-γ release assays in detection of *Mycobacterium tuberculosis* infection with TST in those patients.

2. Patients and methods

A cross-sectional study included 100 SLE patients fulfilling the American college of Rheumatology (ACR) revised classification criteria for SLE [12]. All patients were recruited randomly from the Rheumatology outpatient clinic and the inpatient ward of Internal Medicine and Rheumatology department at Ain Shams University Hospitals. The nature of the present study was explained to all participants. The laboratory and radiological procedures represent standard care and pose no ethical conflicts. Consent from all participants and approval of Research Ethics Committee of Faculty of Medicine, Ain Shams University were obtained.

All patients were subjected to detailed history taking with special emphasis on: age, sex, disease duration, history of tuberculosis, Bacillus Calmette-Guérin (BCG) vaccination and immunosuppressive drug therapy, thorough clinical examination including general, systemic and full rheumatologic examination, assessment of SLE disease activity using the BILAG (British Isles Lupus Assessment Group) disease activity index, categorizing disease activity into five different levels from A to E, where grade A implies very active disease, grade B: moderate disease activity, grade C: mild stable disease, Grade D: no disease activity but the system had previously been affected, Grade E: no current or previous disease activity in the system assessed [13], assessment of the disease damage using the Systemic Lupus International Collaborative Clinics/American College of Rheumatology (SLICC/ACR) Damage Index [14]. Laboratory investigations including complete blood count (CBC) by coulter, erythrocyte sedimentation rate (ESR) first hour by Westergren method, serum creatinine and blood urea nitrogen (BUN) by calorimetric method, urine analysis and Protein/creatinine ratio.

Tuberculin skin test (TST) was performed by injecting 0.1 ml of tuberculin purified protein derivative (PPD) into the inner surface of the forearm. The injection was made with a tuberculin syringe, with the needle bevel facing upward injecting intradermally to produce a pale elevation of the skin (a wheal) 6 to 10 mm in diameter. The skin test reaction was read between 48 and 72 h after administration. The diameter of the indurated area was measured across the forearm (perpendicular to the long axis). An induration of ≥5 mm was considered positive [15].

Interferon gamma (IFN-γ) release assays was done using The QuantiFERON-TB GOLD In-Tube (QFT-GIT) test (QuantiFERON® TB Gold In-Tube; Cellestis Limited, Victoria, Australia) according to the manufacturer's instructions. QFT-GIT was considered positive if the IFN-γ level of nil was ≥8.0 IU/ml and that of TB antigen minus nil was ≥0.35 IU/ml and ≥25% of nil value. The test was considered negative if the IFN-γ level of nil was <8.0 IU/ml and that of TB antigen minus nil was <0.35 and <25% of nil value. The result was considered indeterminate if the IFN-γ level of nil was ≥8.0 IU/ml [16].

Microscopic examination of appropriate specimen for the presence of acid-fast-bacilli (AFB) and culture over Lowenstein Jensen (LJ) medium for tubercle bacilli were done for all patients with positive results of QFT-GIT or TST tests. Also, plain chest radiography (posteroanterior view) was done; cavitary lung lesions, nodules, reticulonodular infiltrates, effusion and hilar lymphadenopathy were considered as abnormalities [17].

Latent TB infection (LTBI) represents a state of a positive TST or QFT-GIT with negative Ziehl–Neelsen stained smears for the presence of AFB and negative culture on LJ medium for tubercle bacilli. While active TB infection was defined by the presence of AFB in Ziehl–Neelsen stained smear or isolation of tubercle bacilli from the specimen cultured on LJ medium [18].

Statistically analysis: was performed using SPSS (Statistical program for social science version 16)**;** description of quantitative variables as mean, standard deviation (SD) and range, description of qualitative variables as number and percentage; Chi-square test was used to compare qualitative variables, unpaired *t*-test was used to compare two independent groups as regard a quantitative variables. P value < 0.05 was considered significant. The concordance between TST and QTF-GIT was evaluated using agreement and the kappa analysis. The tests results were evaluated using Cohen's kappa (k), with k value >0.75 representing good agreement, 0.4–0.75 fair to good agreement and <0.40 poor agreement.

3. Results

Ninety (90%) patients of our participants were females, and 10 (10%) patients were males (F:M 9:1). Their mean age was 29.8 ± 7.9 years (18–55 years). The disease duration was 5.5 ± 5.4 years (0.25–33 years). All studied patient received BCG vaccine during childhood. None of them had a personal or family history of TB. The mean treatment duration of the study participants was 4.29 ± 4.38 years, all of them were on steroids (19.3 ± 7.4 mg/day), 95% were on hydroxychloroquine (HCQ) 374 ± 92.8 mg/day), 75% on azathioprine (101.6 ± 27.1 mg/day), 62% received cyclophosphamide (CYC) with a cumulative mean dose of 4724.2 ± 2878.2 mg and 17% received mycophenolate mofetil (MMF) (2176.5 ± 705.8 mg/day).

Sixty-six (66%) patients had organ damage; with CNS damage being the most common 30%, renal damage in 22% and GIT damage in 2% of patients. The mean damage index was 1.4 ± 1.7 (0–8). Most of the patients were active mostly affecting the renal system (30%) and regarding the BILAG disease activity index, organs with most severe activity were the renal system (30% category A) and the least activity was found in the gastrointestinal system (0% category A). As regard QFT-GIT and TST results, 13% of the patients had a positive QFT-GIT and only 2% had a positive TST (Fig. 1), with a poor agreement between the two tests; The 13 patients with a positive QFT-GIT were TST negative whereas the 2 cases with a positive TST were QFT-GIT negative (Table 1). Microscopic examination and culture of appropriate specimen for the presence of tubercle bacilli were performed for all patients with positive results of QFT-GIT or TST and showed negative results. As regard chest x ray findings 13 (13%) patients had abnormal CXR; 4 of them had bilateral pleural effusion, 4 patients had unilateral pleural effusion, 3 patients had scattered lung opacities with unilateral effusion and 2 patients had lobar lung consolidation.

The SLE patients were classified and compared according to the QFT-GIT test positivity and showed no significant difference as regard age, disease duration, drug history and laboratory data (Table 2). There was no significant difference as regard gender,