Role of Interferon-Gamma in Bronchoalveolar Lavage Fluid on Distinguishing Active Pulmonary Tuberculosis from other Pulmonary Diseases

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Introduction

Tuberculosis (TB) mediated by the airborne pathogen Mycobacterium tuberculosis remains a global pandemic, with around 8.7 million new cases in 2011 [1]. Control of TB is a high priority and becomes one of the international missions after the increase in the number of cases all over the world including the developed countries [2]. The probability of pulmonary tuberculosis disease is based on the experience of close touch with consumptive person and clinical symptoms and imaging results, but acid-fast bacilli (AFB) smear-positive sputum is usually an initial clue in the diagnosis of pulmonary tuberculosis (TB); its approval by the sensitivity of sputum smear is only 40-70% and its slow growth (4-8 weeks) delays the diagnosis and treatment [3, 4].

Fiberoptic bronchoscopy with transbronchial biopsy and bronchoalveolar lavage have proved a valuable tools in the patients with no sputum or not able to excrete the sputum (with sensitivity 48-80%) [5]. Despite the presence of standard diagnostic methods, diagnosis of TB is still problematic. With respect to the prevalence of the disease in Sistan and Balouchestan (the extent of pulmonary TB outbreak in the province is about 32.27 in each 100,000 comparing to 8.73 in 100,000 in the country) [6] and Prompt diagnosis and early treatment of tuberculosis constitute the most effective intervention in controlling and reducing the transmission of M. tuberculosis and since there is no definite laboratory method for TB diagnosis and the low specificity and sensitivity of current diagnostic techniques, it is necessary and useful to find fast and reliable diagnostic methods.

The determination of cytokine concentrations in serum and bronchoalveolar lavage fluid (BALF) may contribute to the diagnosis of tuberculosis since cytokines have been ascribed an important role in TB pathogenesis [7]. The pro-/anti-inflammatory cytokine balance has been shown to play an important role in the pathogenesis and activity of TB including granuloma formation, caseation necrosis and delayed type hypersensitivity. Studies have shown that certain cytokine concentrations in serum as well as bronchoalveolar lavage fluid may also contribute to the diagnosis. Among the major factors in the resulted inflammation, the followings can be implied: interferon-γ (IFN-γ), adenosine deaminase, and TNF, and IFN-γ is a key cytokine in the control of M. tuberculosis infection. It is produced by both CD4- and CD8-type T cells and...
activates macrophages in TB [8] and is one of the main regulators of immune system made by immune cells in response to antigenic and immunological stimulations [7]. IFN-γ increase in much disease for example, granulomatosis disease.

A granuloma is the body's way of dealing with a substance it cannot remove or sterilize. The key association between IFN-γ and granulomas is that IFN-γ activates macrophages so that they become more powerful in killing intracellular organisms.

A granuloma is the body's way of dealing with a substance it cannot remove or sterilize. Infectious causes of granulomas (infections are typically the most common cause of granulomas) include tuberculosis, leprosy, histoplasmosis, cryptococcosis, coccidioidomycosis, blastomycosis and cat. Examples of non-infectious granulomatous diseases are sarcoidosis, berylliosis Wegener's granulomatosis, Churg-Strauss syndrome, pulmonary rheumatoid nodules and aspiration of food and other particulate material into the lung.

IFN-γ induces the anti-mycobacterium inflammatory activity of macrophage which at the time is applied as a diagnostic method in pleural fluid of patients suffering from tubercular pleurisy. In tuberculous pleuritis, diagnosis is established by demonstrating high level of TB markers in pleural fluid (IFN-γ ≥ 140 pg/mL) [3]. In previous studies, IFN-γ levels (blood BALF and peritoneal fluid) were increased in active TB patients [8, 9]. However, there was no significant difference in the serum levels of these cytokines among groups [8]. IFN-γ may be a sensitive and specific marker for the accurate diagnosis of tuberculous peritonitis. The level of IFN-γ may contribute to the accurate differentiation of tuberculosis ascites from non-TB ascites [9]. Elevations of IFN-γ have been found in the affected lung and bloodstream of patients with pulmonary tuberculosis. Shahid reported that measurement of IFN-γ production in blood is helpful to diagnose active tuberculosis, but further research is required [10]. Because the results were inconsistent and incomplete in studies We decided to measure the levels of IFN-γ in bronchoalveolar lavage fluid.

Materials and Methods

This descriptive study took place from 2011 to 2012 at the Ali Ibn-e-Alitaleh hospital, Zahedan on patients who needed bronchoscopy. Participants enrolled in this study gave informed consent. There is no cost to participate in this survey and the study was approved by the hospital ethics committee. Two groups were studied: pulmonary TB patients and pulmonary non-TB patients.

Between 2011 to 2012, in 300 patients needed the fiber optic bronchoscopy as indicated with negative acid-fast sputum smear in triplet, bronchoaveolar fluid was examined in terms of acid-fast staining and cytology. Indications for diagnostic bronchoscopy were suspicion of TB based on clinical and radiological findings and suspicion of lung cancer/obstructive pneumonia atelectasis or reumatologic disease in sputum smear.

Results

During the study period, of the patients undergone bronchoscopy, 88 patients (43 men and 45 women) participated in this study among whom 31 (16 men and 15 women) were diagnosed as pulmonary TB and 57 (27 men and 30 women) pulmonary non-TB. Based on results, mean IFN-γ level in bronchoaveolar fluid was higher in TB patients (2.85±4.17 pg/mL) comparing to non-TB patients (1.21±2.21 pg/mL). Yet, based on Mann Whitney U test, there was no statistically significant difference between the two in terms of IFN-γ level. Then, to find the best predictive value in diagnosing pulmonary TB, ROC curve was drawn by SPSS-20 software for determining bronchoaveolar fluid cut-off point.

At cut off 2.05 pg/mL, sensitivity and specificity were respectively gained 32.3% and 57.9% for pulmonary TB diagnosis. Of TB patients, 10 (32.3%) had IFN-γ level ≥2.05 pg/mL, and 21 (67.7%) had <2.05 pg/mL. Of non-TB patients, 24 (42.1%) had IFN-γ level ≥2.05 pg/mL, and 33 (57.9%) had <2.05 pg/mL. Of 34 patients with
IFN-γ level 2.05 pg/mL ≤10 (29.4%) were pulmonary TB and 24 (70.6%) pulmonary non-TB; while of 54 patients with IFN-γ level <2.05 pg/mL, 21 (38.9%) and 33 (61.1%) were respectively pulmonary TB and pulmonary non-TB.

In differentiating pulmonary active TB from pulmonary non-TB patients, the negative and positive predictive values of IFN-γ level in bronchoaveolar fluid were respectively gained 61.1% and 29.4%. Consequently, there was no need to establish cut off levels for these cytokines, indicating that serum cytokines were not reliable diagnostic tools to distinguish TB from other pulmonary diseases.

Discussion

Mean IFN-γ level in bronchoaveolar fluid of tuberculosis patients was higher than in the non-TB patients but no statistical significance was revealed in the present study.

At cut-off point 2.05 pg/mL, the value of sensitivity and specificity were respectively gained 32.3% and 57.9% which is not high for diagnosing TB and differentiating it from non-TB diseases and indicates that this test is not appropriate for diagnosing pulmonary TB and differentiating it from other pulmonary non-TB diseases. Accordingly, this parameter must not be applied at the time. Animal studies have shown that IFN-γ plays a pivotal and essential role in protective cellular immunity in TB infection [11, 12]. There are many ex-vivo studies showing decreased concentrations of IFN-γ in TB patients [13-16]. Conversely, in previous studies, IFN-γ levels found to be significantly increased in active TB patients [8, 17-20]. However, there was no significant difference in the serum levels of these cytokines among groups. Our results are similar to other previous ones on IFN-γ level in bronchoaveolar fluid. Studies of Tsao et al. and Kupeli et al. again IFN-γ level in pulmonary BT patients’ bronchoaveolar fluid were not different from pulmonary non-BT ones [21, 22].

In a study by Antonangelo et al. IFN-γ level was significantly higher in bronchoaveolar fluid in pulmonary TB patients’ BALF comparing to control group (intact individuals). However, the levels did not have the capability of differentiating TB patients from non-TB ones [23]. Unlike this study, the intact individuals without bronchoalveolar lavage in Turkish patients with smear negative pulmonary tuberculosis. Respir Med. 2002;96(7):536–41.

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Authors’ Contributions

All authors had equal role in design, work, statistical analysis and manuscript writing.

Conflict of Interest

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