Vascular Endothelial Growth Factor Levels in Pleural Fluid and Serum of Patients With Tuberculous Pleural Effusions

To the Editor:

We read with great interest the article by Alatas and co-workers (June 2004), who showed that serum vascular endothelial growth factor (VEGF) levels were increased in patients with active pulmonary tuberculosis, compared to patients with inactive pulmonary tuberculosis and control subjects. They also showed that serum VEGF levels were statistically different before and after treatment in 10 patients who were observed from diagnosis to the completion of treatment. This study suggests that the levels of VEGF in the serum of patients with pulmonary tuberculosis may serve as a marker of disease activity. We believe that the findings of the study of Alatas et al. agree with our data regarding the levels of VEGF in patients with tuberculous pleural effusions.

We studied VEGF levels in the pleural fluid and serum of 15 patients (9 men and 6 women; mean age, 61.26 ± 17.07 years [± SD]) with tuberculous pleural effusions. Fifteen patients (12 men and 3 women; mean age, 69.23 ± 9.98 years) with transudative pleural effusions due to congestive heart failure (CHF) served as control subjects. Tuberculous pleural effusions were diagnosed by positive culture findings for Mycobacterium tuberculosis or a pleural biopsy specimen showing typical epithelial cell caseating granulomas. All CHF patients had a history of heart failure due to systolic dysfunction (ejection fraction < 45%) and presented with bilateral transudative pleural effusions that improved with appropriate treatment with diuretics. The characterization of pleural effusions as transudative or exudative was done according to Light’s criteria.

VEGF levels were measured with a commercially available enzyme-immunosorbent assay kit (Biosource Europe S.A.; Nivelles; Belgium) according to the protocol of the manufacturer. The levels of VEGF in the pleural fluid of patients with tuberculous pleural effusions were significantly higher compared with the levels of VEGF in the pleural fluid of CHF patients (236.4 ± 156.1 pg/mL vs 59.3 ± 26.98 pg/mL, respectively; p = 0.0002). Similar results were observed in the serum of patients with tuberculous effusions and CHF (456.1 ± 295.8 pg/mL vs 217.2 ± 103.8 pg/mL, respectively; p = 0.0003). Interestingly, the levels of VEGF in patients with tuberculous effusions were significantly higher in the serum compared with the pleural fluid (236.4 ± 156.1 pg/mL vs 456.1 ± 295.8 pg/mL, p = 0.017) [Fig 1].

The reports of measurement of VEGF levels in tuberculous pleural effusions are scarce. The elevated levels of VEGF in the tuberculous effusions of our patients confirm the previously available data. Additionally, the elevated levels in the serum of these patients compared with the CHF control subjects suggest that serum VEGF may be a marker of disease activity in patients with tuberculous pleural effusions, as it is in patients with active parenchymal tuberculosis. However, the origin of the VEGF in tuberculous effusions is not clear. In a study by Kraft et al., the VEGF levels in malignant pleural effusions were several-fold higher compared to matched serum samples, being suggestive of a significant local release of this cytokine from the tumor within the pleural cavity. Additionally, VEGF has been reported as a major regulator of angiogenesis with an important role in the development of granulomas. However, VEGF is a potent inducer of vascular permeability, and may thus represent a significant mediator in pleural fluid formation. The significantly higher levels of VEGF in the serum compared to the pleural fluid of our patients are suggestive of the latter role of VEGF, being responsible, at least in part, for the increased vascular permeability that leads to the formation of tuberculous pleural effusions. This is the first study to our knowledge that examines the levels of VEGF both in the pleural fluid and serum of patients with tuberculous pleural effusions, suggesting a possible role of this mediator in the formation of such effusions.

To the Editor:

We would like to express sincere thanks to Dr. Kiropoulos and colleagues for commenting on our recent article in CHEST (June 2004). They presented the results of their study concerning vascular endothelial growth factor (VEGF) levels in the pleural fluid of tuberculous patients. We discussed their results and would like to raise some questions and comments.

REFERENCES

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Figure 1. VEGF levels. PFTBC = pleural fluid in tuberculosis patients; PFCHF = pleural fluid in CHF patients; STBC = serum in tuberculosis patients; SCHF = serum in CHF patients.
First, there are few studies about the VEGF levels in tuberculous pleural effusions, as Dr. Kiropoulos mentioned. Momi et al and Hamed et al measured VEGF levels both in the serum and pleural fluid of tuberculous pleurisy patients. They found elevated VEGF levels both in the serum and pleural fluid of tuberculous pleurisy patients compared with congestive heart failure patients. In congestive heart failure patients, both of the studies reported higher VEGF levels in serum than in pleural fluid, as expected.

Second, pleural fluid VEGF levels in tuberculous pleurisy patients were lower than the respective serum levels found in the study by Kiropoulos. However, in the studies by Momi et al and Hamed et al, VEGF levels in pleural fluid were higher than those in the serum of tuberculous pleurisy patients. This is an important discrepancy since the proposed mechanism for the increase in VEGF levels in the pleural fluid may be strictly different. The proposed mechanisms for the increase of VEGF in pleural fluid are increased vascular permeability, and local production by mesothelial cells and/or pleural macrophages. Another important issue is the standardization of tuberculous patients. A tuberculous pleurisy patient may also have a tuberculous lesion in the lung parenchyma. In this situation, VEGF may be secreted from active tuberculosis lesions beside those in the pleura.

In conclusion, while we agree with Dr. Kiropoulos on the possible role of VEGF as a mediator of pleural fluid formation, we think that well-standardized studies with more tuberculous patients are needed in order to clarify the underlying mechanisms. We appreciate the contributions by Dr. Kiropoulos.

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At Least Three FEV1 Blows Are Required at Each Time Point During the Assessment of Bronchial Hyperresponsiveness
To the Editor:

Bronchoprovocation tests are used routinely in clinical practice and research to detect and quantify the presence of bronchial hyperresponsiveness. Histamine, methacholine, and 5′-adenosine monophosphate (AMP) are some of the bronchoprovocative agents used to test bronchial hyperresponsiveness. After obtaining the baseline FEV1 value, subjects are asked to inhale increasing concentrations of bronchoprovocative agents with a dosimeter, until the postchallenge FEV1 drops by 20% from the baseline value (measured as provocative dose causing a 20% fall in FEV1 [PD20], or provocative concentration causing a 20% fall in FEV1). According to American Thoracic Society guidelines, subjects are asked to perform at least three FEV1 maneuvers at each time point after administering the bronchoprovocative dose. This may mean performing up to 75 forced expiratory maneuvers over a period of 1 h, which can be very tiring to many patients undergoing this test.

Cockcroft and colleagues have described test-shortening procedures for bronchial challenge, in which they have recommended a single forced expiratory maneuver at each time point following administration of the bronchoprovocative substance. However, because of the variability between FEV1 values in the same subject when performed at the same time, using only one forced expiratory maneuver may not be reliable to obtain the highest FEV1 value.

We aimed to study whether three forced expiratory blows are necessary at each time point following the bronchoprovocative challenge and whether the first or second forced expiratory maneuver gives the highest FEV1 value >90% of the time. We conducted a study in 12 subjects who underwent two bronchoprovocation tests on separate days at least a week apart with AMP and determined how frequently the best FEV1 value was obtained during the first, second, and third forced expiratory maneuvers after sufficient motivation to give their best effort at each of the three blows. These were recorded as best, second best, and third best (highest to lowest FEV1 values), and their corresponding blow numbers were recorded (first blow, second blow, and third blow). The first blow produced the best FEV1 in 43.49% of the times, while the second and third blows produced the best FEV1 values 24.59% and 31.92% of the times, respectively. Only using one blow (as suggested by Cockcroft and colleagues) would have missed the best FEV1 value 56.51% of the times, while using two FEV1 blows would have missed the best FEV1 value 31.92% of the times. We therefore conclude that in order to obtain reliable FEV1 values during bronchoprovocation testing, at least three forced expiratory blows are required at each time point.

Asking the subject to perform only one forced expiratory blow would give unreliable FEV1 values, which would likely give false PD20 values.

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