Association Between Bronchiectasis, Systemic Inflammation, and Tumor Necrosis Factor α

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OBJECTIVE: The relationship between systemic inflammation and different measures of bronchiectasis severity has not been described. The objective of this study was to analyze the relationship between plasma concentrations of tumor necrosis factor α (TNF-α), as a marker of systemic inflammation, and some commonly used criteria for quantifying bronchiectasis severity in clinically stable patients whose disease was not caused by cystic fibrosis.

PATIENTS AND METHODS: Sixty-eight clinically stable patients with bronchiectasis and 19 age- and sex-matched healthy control subjects were included in the study. Data on disease history, symptoms, severity, functional variables, sputum volume, and microbiological cultures, laboratory findings, and other indicators of disease course were collected. Plasma concentrations of TNF-α were measured using high-resolution enzyme-linked immunosorbent assay.

RESULTS: Plasma concentrations of TNF-α were higher in patients than controls (8.28 vs 5.67 pg/mL; P<0.001). This observation correlated with other markers of systemic inflammation such as erythrocyte sedimentation rate (r=0.42; P<0.001), C-reactive protein (r=0.45; P<0.001), and percentage of peripheral blood neutrophils (r=0.45; P<0.001). Patients with high plasma concentrations of TNF-α (>8.1 pg/dL) had more severe disease (5.19 vs 3.21; P<0.001), were more likely to have respiratory failure (37.5% vs 8.3%; P<0.003), and a higher rate of Pseudomonas aeruginosa colonization (34.3% vs 8.3%; P=0.008).

CONCLUSIONS: High plasma concentrations of TNF-α were associated with several criteria usually used to assess severity of bronchiectasis in clinically stable patients with disease not caused by cystic fibrosis.

Key words: Bronchiectasis. Tumor necrosis factor α. Pseudomonas aeruginosa.

Bronquiectasias, inflamación sistémica y factor de necrosis tumoral alfa: factores asociados

OBJETIVO: La relación existente entre la presencia de inflamación sistémica y los diferentes parámetros de gravedad en pacientes con bronquiectasias no ha sido descrita. El objetivo del estudio ha sido analizar la relación entre las concentraciones plasmáticas de factor de necrosis tumoral alfa (pTNF-α), como marcador de inflamación sistémica, y algunos criterios de gravedad comúnmente utilizados en pacientes con bronquiectasias, en fase de estabilidad clínica, no debidas a fibrosis quística.

PATIENTES Y MÉTODOS: Se incluyó en el estudio a 68 pacientes con bronquiectasias clínicamente estables y 19 controles sanos ajustados según edad y sexo. Se recogieron datos referentes a antecedentes patológicos, síntomas, extensión, variables funcionales, volumen de esputo y aspectos microbiológicos, analíticos e evolutivos. Las concentraciones de pTNF-α se analizaron utilizando un método de enzimoinmunanálisis de alta resolución.

RESULTADOS: Se observó una mayor concentración de pTNF-α en los pacientes que en los controles (8.28 frente a 5.67 pg/mL; p = 0.001), que se correlacionó con otros parámetros de inflamación sistémica como la velocidad de sedimentación globular (r = 0.42; p = 0.001), la proteína C reactiva (r = 0.45; p = 0.001) y el porcentaje de neutrófilos periféricos (r = 0.45; p = 0.001). Los pacientes con concentraciones elevadas de pTNF-α (> 8.1 pg/dL) presentaron mayor extensión de la enfermedad (5.19 frente a 3.21; p = 0.001), mayor probabilidad de presentar insuficiencia respiratoria (el 37.5 frente al 8.3%; p = 0.003) y mayor porcentaje de colonizaciones por Pseudomonas aeruginosa (el 34.3 frente al 8.3%; p = 0.008).

CONCLUSIONES: Las concentraciones elevadas de pTNF-α se asocian a varios parámetros comúnmente utilizados para valorar la gravedad en pacientes con bronquiectasias clínicamente estables y no debidas a fibrosis quística.


Introduction

Bronchiectasis is usually described as a chronic lung disease characterized by irreversible bronchial dilation as a result of a vicious pathogenic circle comprising...
abnormalities in mucociliary clearance, inflammation, and infection of the bronchial mucosa. The affected patients have chronic production of sputum, usually with a purulent appearance, repeated exacerbations, and an obstructive breathing pattern that responds poorly to bronchodilators. In the end stages of the disease, progressive dyspnea dominates the clinical picture, with a substantial accompanying decrease in the patients’ quality of life.

The bronchial inflammation present in bronchiectasis is characterized by a preponderance of mononuclear cells and neutrophils. In patients with bronchiectasis, there have been reports of high concentrations of certain proinflammatory cytokines such as tumor necrosis factor α and interleukins (IL) 6 and 8 in both sputum and bronchoalveolar lavage. Although it is accepted that inflammatory response is compartmentalized to the lung, some studies have found a significant increase in the circulating concentration of certain systemic inflammatory markers such as acute phase reactants and inflammatory mediators, even during phases of clinical stability. It has been postulated that the presence of systemic inflammation in certain lung diseases could arise because local inflammatory markers “overflow” in patients with a higher degree of bronchial or pulmonary inflammation. Some authors have therefore suggested that circulating inflammatory markers might faithfully reflect the most severe forms of these diseases.

TNF-α is a proinflammatory cytokine synthesized and secreted by monocytes and macrophages. It has a range of properties, such as chemotraction of neutrophils at the site of inflammation and upregulation of the expression of other chemokines with a function similar to that of IL-8. It is generally accepted that TNF-α is an essential mediator in the inflammatory cascade of a range of lung diseases and that it is able to serve as a marker of progression or prognosis in certain diseases, such as pneumonia, or cystic fibrosis. There is no single marker of the severity of bronchiectasis, and so a range of criteria, including clinical manifestations, respiratory function variables, and extent of disease, have been used. The relationship between disease severity and the profile of circulating inflammatory cytokines has not been established in patients with bronchiectasis.

The objective of the present study was to analyze the relationship between the plasma concentrations of TNF-α as a marker of systemic inflammation and a set of widely used criteria of disease severity in a broad group of patients with clinically-stable bronchiectasis not caused by cystic fibrosis.

Patients and Methods

Study Population

All patients diagnosed with bronchiectasis not caused by cystic fibrosis were initially included in the study, regardless of the extent of disease. To be included, patients had to have clinically stable disease—that is, they had to have been free of exacerbation for at least 4 weeks from the start of the study—and have a history of tobacco consumption of fewer than 10 pack-years. The exclusion criteria were as follows: traction bronchiectasis due to advanced fibrosis; active smoking; a history of a disease other than bronchiectasis that might substantially influence plasma TNF-α concentration, such as kidney failure, tumors, active infections, heart failure, and other systemic inflammatory diseases; asthma according to the Global Initiative for Asthma (GINA) criteria; difficulty following the study protocol due to substantial physical or psychiatric disability; and long-term treatment with immunodepressants or oral corticosteroids. Twenty-three patients (33.8%) were receiving inhaled corticosteroid therapy (doses of 500-1000 µg/d of fluticasone or equivalent doses of budesonide). No patient was receiving long-term macrolide therapy.

The control group comprised 19 healthy volunteers whose age and sex distribution showed no statistical differences to that of the patients. We considered healthy controls to be individuals without any relevant diseases in their medical history who had never smoked, had no respiratory symptoms, were not receiving bronchodilator or corticosteroid therapy, and had no pathological spirometric and chest radiographic findings.

Our local ethics committee approved the present study and all patients were informed of its goals.

Diagnosis of Bronchiectasis

The diagnosis of bronchiectasis was established in all cases by means of a high-resolution computed tomographic scan of the chest with 1-1.5 mm slices every 10 mm and subsequent digital reconstruction of the image according to the criteria of Naidich et al. Patients whose last scan had been done more than 24 months before the start of the study underwent a new scan to update the estimation of the extent of bronchiectasis. The extent and radiologic characteristics of bronchiectasis were assessed by means of a simplified version of the Bhalla score, which has been used by our group in other studies.

Assessment of the Severity of Bronchiectasis

There is no single criterion for assessing the severity of bronchiectasis. In the present study, we considered a patient to have severe disease when at least one of the following was present: greater bronchial airflow obstruction, chronic colonization by Pseudomonas aeruginosa, respiratory failure, greater extent of lung involvement, lower quality of life, higher number of exacerbations, and greater severity of clinical symptoms (more severe dyspnea or more sputum production per day).

Study Protocol

In addition to the demographic and anthropometric data, relevant medical history, and smoking habit, the following data were prospectively collected during 2003 on the day of the patients’ appointment:

1. Clinical Variables. The mean sputum production per day was calculated in milliliters according to a procedure used by our group in previous studies. Dyspnea at rest was quantified according to the scale proposed by the Medical Research Council and modified by the American Thoracic Society. We considered the results of a symptoms diary in which patients recorded the number of days with cough and wheezing, as well as the number of on-demand daily inhalations of β-adrenergic agents used in the month prior to the visit, defining regular cough or wheezing as the presence of these symptoms on more than half the days (assessed as dichotomous variables).

2. Health-related quality of life. This variable was quantified with the validated Spanish version of the St George’s Respiratory Questionnaire.

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3. Respiratory function variables. Oxygen saturation (SaO₂) was determined, and patients underwent spirometry to measure forced expiratory volume in 1 second (FEV₁) and forced vital capacity (FVC). The lung function tests were repeated 15 minutes after bronchodilation with 200 µg of salbutamol (bronchodilator test). Airflow obstruction was defined as FEV₁/FVC below 70% and respiratory failure as the SaO₂ below 90%. All lung function tests were performed first thing in the morning and overseen by qualified personnel.

4. Laboratory variables. A sample of peripheral blood was collected, both from patients and from healthy controls, between 8 AM and 10 AM for neutrophil counts and measurement of the erythrocyte sedimentation rate (ESR) (mm) in the first hour, fibrinogen concentration (mg/dL), serum concentrations of C-reactive protein (CRP) (mg/dL), immunoglobulin A and G concentrations (g/L), and plasma concentrations of TNF-α and IL-8 (pg/mL).

5. Exacerbations. Data on the number of exacerbations in the 6 months prior to the visit were also collected. An exacerbation was defined as the presence of at least 3 respiratory symptoms (cough, dyspnea, hemoptysis, increased volume or purulence of sputum, or chest pain), lasting at least 24 hours, regardless of whether the patient also had fever, radiologic abnormalities, or systemic manifestations.

6. Microbiological variables. Finally, 6 pairs of sputum samples were collected in the 6 months prior to the visit (2 samples per month) for microbiological study, which included Gram staining and culture in standard or special media according to the suspicion of specific microorganisms. Chronic colonization by P. aeruginosa was considered present when at least 10³ colony forming units per mL were observed in valid sputum samples (<10 epithelial cells and >25 leukocytes per field) in at least 3 sputum samples taken in different months not corresponding to an exacerbation period.

In the case of the appearance of an exacerbation during the 4 weeks prior to the inclusion of the patient in the study, we waited for at least 4 weeks after the end of treatment of the exacerbation before enrolling the patient.

Measurement of Plasma Concentration of TNF-α and Interleukin-8

The plasma concentrations of TNF-α and IL-8 were analyzed in duplicate by high-resolution enzyme-linked immunosorbent assay (ELISA) according to the instructions of the manufacturer (Bender MedSystems Inc, Burlingame, California, USA). Calibration curves were constructed from the data derived from the standard samples and the reference plasma. These curves were used to calculate TNF-α and IL-8 concentrations in patients and the control group using appropriate software. The valid concentration was taken to be that obtained by calculating the simple arithmetic mean of the 2 measurements taken simultaneously in the same individual. The assay sensitivity was less than 3 pg/mL for TNF-α and 0.7 pg/mL for IL-8. The coefficients of variation were 8.5% (intra-assay) and 9.8% (inter-assay) for TNF-α and 5% (intra-assay) and less than 10% (interassay) for IL-8.

Statistical Analysis

The statistical package SPSS version 9.0 (SPSS, Chicago, Illinois, USA) for Windows was used. All data were presented as means (SD) in the case of quantitative variables and absolute values and percentages of the total in the case of qualitative or dichotomous variables. A normal distribution was confirmed using the Kolomogorov-Smirnov test. For variables without a normal distribution, the corresponding nonparametric tests were used. The t test or the Mann-Whitney U test was used for comparison of 2 means, and the χ² test with the Yates correction was used for the comparison of 2 dichotomous or qualitative variables. Correlations between variables were analyzed with the Spearman correlation coefficient. Given that plasma TNF-α concentrations were distributed normally in healthy control subjects, abnormally high concentrations of plasma TNF-α were defined as those that exceeded the upper 95% confidence interval (mean + 1.96 SD) of the concentration distribution of healthy control subjects (8.1 pg/mL). In patients or control subjects in whom plasma TNF-α or IL-8 concentrations were below the levels of sensitivity (undetectable values), this was considered valid for subsequent calculation of the minimum concentration value for the assay. A logistic regression analysis was used to determine the independent variables that were associated with elevated plasma TNF-α concentrations (the dependent variable). The degree of association was analyzed by means of the odds ratio (OR) and its corresponding 95% confidence interval. Independent variables that were statistically different in the bivariate study comparing the group of patients with elevated plasma TNF-α concentrations (>8.1 pg/mL) with those without elevated concentrations were entered into the logistic regression model. Statistical significance was established at P less than .05.

Results

Of the 106 patients who had smoked less than 10 pack-years, the following patients were excluded: 1 patient with rheumatoid arthritis, 3 patients receiving long-term anti-inflammatory treatment, 2 patients with other systemic inflammatory diseases, 2 patients with kidney failure, 23 patients with suspected asthma, and 5 patients unable to comply with the study protocol due to serious deterioration in their physical and mental condition. Two patients refused to participate in the study. The characteristics of the 68 patients finally included and the 19 health control subjects are shown in Table 1. Fourteen patients (20.1%) had chronic colonization by P. aeruginosa. The majority of patients had moderate airflow obstruction (mean FEV₁, 62.8%) and a significant decrease in SaO₂ (mean, 94.1%). The healthy subjects had normal FVC, FEV₁, and SaO₂ values.

The concentrations of some systemic inflammatory markers, such as ESR, CRP, and fibrinogen, were significantly higher in patients than in control subjects. There were no significant differences in the percentages of neutrophils or the immunoglobulin A and G or IL-8 concentrations between the 2 groups (Table 2). Eleven patients (16.2%) and 1 healthy subject (5.3%) had undetectable concentrations of plasma TNF-α (below the sensitivity of the assay). Thirty-six patients (53%) and 6 control subjects (31.6%) had undetectable concentrations of IL-8.

In the patient group, plasma TNF-α concentrations were significantly associated with other markers of systemic inflammation: ESR (r=0.42, P=.001) and CRP (r=0.45, P=.001) and the percentage of neutrophils (r=0.45, P=.001), as well as the score for extent of bronchiectasis (r=0.38, P=.004) (Figure 1).

The plasma TNF-α concentration was abnormally high (>8.1 pg/mL) in 32 of the 68 patients (47.1%). These
patients had greater airflow obstruction (FEV₁, 56.9% vs 67.5%, \(P=0.04\)), greater extent of bronchiectasis (5.19 vs 3.21, \(P=0.001\)), as well as a higher proportion of cystic formations (40.6% vs 16.7%, \(P=0.04\)); presence of respiratory insufficiency (37.5% vs 8.3%, \(P=0.003\)), and a higher proportion of chronic colonization by \(P\) aeruginosa (34.3% vs 8.3%, \(P=0.008\)) than the remaining patients (Table 3). However, only the presence of respiratory failure (OR, 5.57), chronic colonization by \(P\) aeruginosa (OR, 4.47), and extent of bronchiectasis (OR, 1.46) were independently associated with elevated plasma TNF-\(\alpha\) concentrations after multivariate adjustment using a logistic regression model (Table 4). There were no significant differences in age, sex, body mass index, clinical variables, quality-of-life variables, on-demand use of \(\beta\)-adrenergic agents, or number of exacerbations.

### Table 1
Baseline Characteristics of Patients With Bronchiectasis and Healthy Control Subjects

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Bronchiectasis (n=68)</th>
<th>Healthy Controls (n=19)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, males</td>
<td>69.8 (8.5)</td>
<td>68.4 (10.1)</td>
<td>NS</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>28.3 (4.1)</td>
<td>27.9 (6.2)</td>
<td>NS</td>
</tr>
<tr>
<td>FEV₁, mL</td>
<td>1416 (550)</td>
<td>1993 (273)</td>
<td>.0001</td>
</tr>
<tr>
<td>FEV₁, % predicted</td>
<td>62.8 (19.9)</td>
<td>85 (10.7)</td>
<td>.003</td>
</tr>
<tr>
<td>FVC, mL</td>
<td>2334 (708)</td>
<td>2957 (354)</td>
<td>.0001</td>
</tr>
<tr>
<td>FVC, % predicted</td>
<td>78.8 (15.7)</td>
<td>99 (9.9)</td>
<td>.004</td>
</tr>
<tr>
<td>SaO₂, %</td>
<td>94.1 (3.8)</td>
<td>97.3 (1.7)</td>
<td>.001</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; NS, not significant; SaO₂, oxygen saturation.

### Table 2
Systemic Inflammatory Markers in Patients and Healthy Control Subjects

<table>
<thead>
<tr>
<th>Neutrophils, %</th>
<th>Bronchiectasis (n=68)</th>
<th>Healthy Controls (n=19)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen, mg/dL</td>
<td>370.2 (69.5)</td>
<td>325.1 (64.3)</td>
<td>.04</td>
</tr>
<tr>
<td>ESR, mm/h</td>
<td>19.2 (12.1)</td>
<td>6.95 (3.6)</td>
<td>.01</td>
</tr>
<tr>
<td>CRP, mg/dL</td>
<td>0.63 (0.53)</td>
<td>0.16 (0.3)</td>
<td>.001</td>
</tr>
<tr>
<td>IgA, mg/dL</td>
<td>357 (142)</td>
<td>324 (127)</td>
<td>NS</td>
</tr>
<tr>
<td>IgG, mg/dL</td>
<td>1242 (2418)</td>
<td>1060 (2107)</td>
<td>NS</td>
</tr>
<tr>
<td>TNF-(\alpha), pg/mL</td>
<td>8.28 (1.93)</td>
<td>5.67 (1.25)</td>
<td>.001</td>
</tr>
<tr>
<td>IL-8, pg/mL</td>
<td>4.47 (3.5)</td>
<td>4.31 (2.4)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Ig, immunoglobulin; IL-8, interleukin-8; NS, not significant; TNF-\(\alpha\), tumor necrosis factor \(\alpha\).

Figure. Correlation between plasma concentrations of tumor necrosis factor \(\alpha\) (pTNF-\(\alpha\)) and other markers of systemic inflammation or extent of disease in patients with bronchiectasis (n=68). Spearman correlation coefficient between pTNF-\(\alpha\) concentrations and (A) percentage of neutrophils in peripheral blood; (B) erythrocyte sedimentation rate (ESR); (C) C-reactive protein (CRP) concentration; and (D) score for extent of bronchiectasis in the high-resolution computed tomography scan (HR-CT).
TABLE 3
Comparison Between Patients With Elevated Plasma Concentrations of Tumor Necrosis Factor α (>8.1 pg/mL) and Normal or Low Concentrations (<8.1 pg/mL)*

<table>
<thead>
<tr>
<th></th>
<th>&gt;8.1 pg/mL (n=32)</th>
<th>&lt;8.1 pg/mL (n=56)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR-CT score</td>
<td>5.19 (2.4)</td>
<td>3.21 (1.6)</td>
<td>.001</td>
</tr>
<tr>
<td>Cystic formations</td>
<td>13 (40.6%)</td>
<td>6 (16.7%)</td>
<td>.03</td>
</tr>
<tr>
<td>Rescue β-adrenergic agents, puffs/wk</td>
<td>4.52 (4.2)</td>
<td>3.82 (5.1)</td>
<td>NS</td>
</tr>
<tr>
<td>Long-term antibiotic therapy</td>
<td>4 (12.5%)</td>
<td>3 (8.3%)</td>
<td>NS</td>
</tr>
<tr>
<td>Regular cough</td>
<td>14 (43.7%)</td>
<td>13 (36.1%)</td>
<td>NS</td>
</tr>
<tr>
<td>Regular wheezing</td>
<td>11 (34.4%)</td>
<td>10 (27.7%)</td>
<td>NS</td>
</tr>
<tr>
<td>Sputum volume, mL</td>
<td>22.6 (19.2)</td>
<td>19.3 (23.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Dyspnea, MRC score</td>
<td>1.9 (1.1)</td>
<td>1.6 (0.8)</td>
<td>NS</td>
</tr>
<tr>
<td>SGRQ, overall score</td>
<td>46.6 (20.4)</td>
<td>43.6 (16.9)</td>
<td>NS</td>
</tr>
<tr>
<td>FEV1, %</td>
<td>56.9 (17.7)</td>
<td>67.5 (20.5)</td>
<td>.04</td>
</tr>
<tr>
<td>FVC, %</td>
<td>74.1 (13.9)</td>
<td>80.9 (15.9)</td>
<td>NS</td>
</tr>
<tr>
<td>FEV1/FVC &lt;70%</td>
<td>25 (78.1%)</td>
<td>18 (50%)</td>
<td>.02</td>
</tr>
<tr>
<td>Respiratory insufficiency</td>
<td>12 (37.5%)</td>
<td>3 (8.3%)</td>
<td>.003</td>
</tr>
<tr>
<td>Chronic colonization by</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P aeruginosa</td>
<td>11 (34.3%)</td>
<td>3 (8.3%)</td>
<td>.008</td>
</tr>
<tr>
<td>Exacerbations*</td>
<td>1.2 (1.2)</td>
<td>1.2 (1.6)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Abbreviations: FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; HR-CT, high-resolution computed tomography; MRC, Medical Research Council; NS, not significant; SGRQ, St. George’s Respiratory Questionnaire.
*Data are presented as mean (SD) or number of patients (%).

On the other hand, we found that fibrinogen concentration was weakly but significantly associated with the extent of bronchiectasis (r=0.21; P=.04) and that both ESR and CRP were associated with chronic colonization by P aeruginosa (r=0.23, P=.03 and r=0.27, P=.03, respectively) but not with any other clinical or respiratory function variables or markers of progression. Plasma concentrations of IL-8 were not associated with any of the study variables.

Discussion

According to our results, patients with clinically stable bronchiectasis had high peripheral concentrations of certain systemic inflammatory markers compared to healthy control subjects. Plasma concentrations of TNF-α correlated with other markers of systemic inflammation such as CRP, ESR, and the percentage of circulating neutrophils, as well as with more extensive bronchiectasis. Furthermore, patients with abnormally high plasma TNF-α concentrations had more extensive bronchiectasis, greater airway obstruction, and greater probability of chronic colonization by P aeruginosa or respiratory failure. However, other markers of systemic inflammation such as fibrinogen, CRP, and ESR only showed a weak correlation (or no correlation in the case of IL-8) with these bronchiectasis variables.

Although there is evidence that the compartmentalization of inflammatory response to the lung occurs in bronchiectasis,8,9 some authors have reported an increase in the peripheral concentration of some inflammatory markers that reflect systemic inflammation in patients with bronchiectasis, even outside the exacerbation periods. Angrill et al8 found that normal IL-6 and IL-1b concentrations were present in the peripheral blood of only 53% and 63% of their patients, respectively, with clinically stable bronchiectasis, and that only 37% had normal serum concentrations of TNF-α, with a mean concentration of 20 pg/mL, although the authors did not investigate whether these patients showed any characteristics that might differentiate them from the rest. In addition, Wilson et al10 observed an increase in the systemic concentration of certain acute phase reactants such as ESR, CRP, and some immunoglobulins in 35% to 40% of their patients with clinically stable bronchiectasis, although that study did not include any control group of healthy subjects. The findings of the present study are in agreement with previous studies on these points. In effect, we found that some acute-phase reactants such as ESR, CRP, and fibrinogen were abnormally elevated in the serum of patients with bronchiectasis with respect to the control group. The plasma concentrations of TNF-α were detectable in most patients (83.8%) and control subjects (94.7%). This high percentage of patients with detectable levels can essentially be explained by the extensive disease in our patients, given that those with bronchiectasis confined to a single pulmonary lobe were not included in our study, and by the high sensitivity of the ELISA used. The plasma concentration of TNF-α was higher in patients with bronchiectasis than in healthy control subjects and was significantly correlated with other systemic inflammatory markers. According to the established cutoff of 8.1 pg/mL, 47.1% of the patients with bronchiectasis had an abnormally high concentration of TNF-α in plasma. This observation could be related to the persistence of substantial local inflammation even during phases of

TABLE 4
Logistic Regression Analysis: Factors Independently Associated With Elevated Plasma Concentrations of Tumor Necrosis Factor α (>8.1 pg/mL) in Patients With Bronchiectasis

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>SE</th>
<th>Wald</th>
<th>df</th>
<th>P</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>-2.8</td>
<td>0.75</td>
<td>14.5</td>
<td>1</td>
<td>.0001</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Respiratory insufficiency</td>
<td>1.7</td>
<td>0.82</td>
<td>4.4</td>
<td>1</td>
<td>.037</td>
<td>5.57</td>
<td>1.58-33.4</td>
</tr>
<tr>
<td>Chronic colonization by P aeruginosa</td>
<td>1.5</td>
<td>0.72</td>
<td>4.3</td>
<td>1</td>
<td>.039</td>
<td>4.47</td>
<td>1.08-18.47</td>
</tr>
<tr>
<td>HR-CT Score</td>
<td>0.38</td>
<td>0.16</td>
<td>5.5</td>
<td>1</td>
<td>.019</td>
<td>1.46</td>
<td>1.07-2.01</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; df, degrees of freedom; HR-CT, high-resolution computed tomography; OR, odds ratio.
clinical stability, in turn explaining the progressive destruction of the lung parenchyma observed at times during the course of the disease in these patients. In any case, we should mention that the limited number of control subjects included in our study might lead to an error in establishing the upper limit of normal. Whatever the explanation, the effect of greater or lesser systemic inflammation on the severity or progression of bronchiectasis remains unknown. It has been postulated that the presence of systemic inflammatory markers could be due to overflow of local markers in situations of severe bronchial inflammation. Thus systemic expression of local inflammation could be a reliable reflection of the overall severity of bronchiectatic disease, as seems to occur in other lung diseases such as pneumonia or adult respiratory distress syndrome. Interestingly, in patients with bronchiectasis, some authors have reported correlations between certain markers of systemic inflammation such as CRP, ESR, endothelin-1, E-selectin, and intercellular adhesion molecules, and certain clinical and respiratory function variables and extent of bronchiectasis. We preferred to quantify the concentration of TNF-α in plasma, given that it is known to be a key molecule in the development and maintenance of inflammation in many inflammatory diseases or lung infections, and has even been associated with severe forms of bronchiectasis caused by cystic fibrosis with *P. aeruginosa* colonization. Indeed, our findings showed a positive correlation between plasma TNF-α concentrations and the presence of some commonly used variables for stratifying the severity of bronchiectasis not caused by cystic fibrosis, such as the extent of disease, presence of cystic formations, presence of airway obstruction, presence of chronic colonization by *P. aeruginosa*, or presence of respiratory failure. Moreover, these correlations were stronger than those found for other markers of systemic inflammation such as fibrinogen, CRP, or ESR. In any case, all of these variables, only the presence of respiratory failure, chronic colonization by *P. aeruginosa*, and the extent of disease were independent predictors of an elevated plasma concentration of TNF-α after multivariate adjustment. The elimination from the equation of the remaining variables, such as cystic formations or the presence of airway obstruction, was probably accounted for by collinearity with other variables of greater statistical weight, such as chronic colonization by *P. aeruginosa* or the extent of disease.

Some authors have reported that hypoxia might activate TNF-α synthesis and thus complete a vicious circle that would explain the relationship found between the presence of respiratory failure and elevated plasma concentrations of TNF-α. Some studies have also found correlations between certain markers of systemic inflammation, such as endothelin-1, E-selectin, and vascular cell adhesion molecule, and the extent of bronchiectasis. Our study is thus the first to show that this relationship is also present for concentrations of TNF-α in peripheral blood. Finally, our results are consistent with those of other studies in terms of the relationship between greater systemic inflammation, quantified through IL-6 concentration, and TNF-α itself, in patients with bronchiectasis due to cystic fibrosis and the presence of chronic colonization by *P. aeruginosa*.

We also observed that TNF-α plasma concentrations tended to be higher in patients with the greatest deterioration in both their clinical state and quality of life and with a greater number of exacerbations, although this trend was not significant. It may be that this finding is conditioned by the patient’s subjective perception when interpreting clinical manifestations and quality of life as these variables can be influenced by many other external factors and by the retrospective nature of data collection regarding the number of exacerbations in the 6 months prior to the start of the study. Finally, it is important to note that, in our sample, 33.8% of the patients were taking medium or high doses of inhaled corticosteroids, a fact which might lead to lower concentrations of plasma TNF-α given the potent anti-inflammatory effects of these drugs.

We conclude that, according to our results, plasma TNF-α concentrations are more closely correlated with different variables commonly used in assessing the severity of disease than are other systemic inflammatory markers in clinically stable patients with bronchiectasis not caused by cystic fibrosis. Recently, it has been reported that an inflammatory airway disease such as asthma has benefited from therapy with TNF-α antagonists, particularly in the most severe manifestations. Thus, further studies are required to assess the clinical and therapeutic potential of the role of TNF-α in determining the severity and course of bronchiectasis.

**REFERENCES**


