Relationship between disease severity and inflammatory markers in cystic fibrosis

Dieter Y Koller, Manfred Götz, Claudia Wojnarowski, Irmgard Eichler

Abstract
To evaluate the clinical use of measuring neutrophil, lymphocyte, and eosinophil activities, serum myeloperoxidase (MPO), soluble interleukin-2 receptors (sIL-2R), and eosinophil cationic protein (ECP) were measured in 98 patients with cystic fibrosis and in 85 healthy children. Serum concentrations of MPO, sIL-2R, and ECP were increased in patients with cystic fibrosis (median 807 μg/l, 4452 pg/ml, 48.8 μg/l, respectively) compared with the controls (median 319 μg/l, 2743 pg/ml, 9.4 μg/l). ECP concentrations, but not serum MPO or sIL-2R, were significantly related to disease severity assessed by the Shwachman-Kulczycki score and by pulmonary function (forced expiratory volume in one second % predicted). Neither ECP nor sIL-2R was influenced by Pseudomonas aeruginosa infection, acute pulmonary exacerbation, or atopy. Serum MPO, however, was strongly correlated with acute pulmonary exacerbation. In the light of these findings the measurement of serum ECP might thus be used for clinical monitoring and for assessing disease severity in cystic fibrosis. The measurement of serum MPO and sIL-2R did not correlate with the disease severity.

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Keywords: cystic fibrosis, eosinophil cationic protein, myeloperoxidase, soluble interleukin 2 receptor.

The most frequent clinical manifestation in patients with cystic fibrosis is progressive pulmonary destruction due to chronic endobronchial infection. There is increasing evidence that immune mediated inflammation also contributes to progressive pulmonary tissue damage. Knowledge about the immune processes in cystic fibrosis allows us to analyse and quantitate cells or cell products suggested to be involved in the pathology and to follow changes as a reflection of pulmonary disease in cystic fibrosis. Eosinophils appeared to play a minor part until the demonstration of highly activated eosinophils measured by eosinophil cationic protein (ECP) concentrations in patients with cystic fibrosis. In addition, assessment of pulmonary inflammation is possible by measuring cell products in blood samples. Persistence of endobronchial infection may cause an excessive immune response, reflected by high concentrations of immunoglobulins, immune complexes, and neutrophil products—for example, elastase and myeloperoxidase (MPO). Concentrations of soluble interleukin-2 receptors (sIL-2R), a marker of T lymphocyte activation, have been shown to be increased even before any clinical evidence of lung inflammation due to infection in cystic fibrosis. Thus pulmonary manifestations in cystic fibrosis may be considered as an inflammatory disease.

In this study, the activation of neutrophils, lymphocytes, and eosinophils was examined by measuring concentrations of MPO, sIL-2R, and ECP in serum samples from healthy subjects and from patients with cystic fibrosis of variable disease severity to determine their role in the assessment of the clinical disorder.

Patients and methods

PATIENTS AND CONTROLS

Ninety eight patients with cystic fibrosis from the Cystic Fibrosis Care Center Vienna were studied (mean (SD) age 11.0 (7.69) years; 45 boys and 53 girls). Fifty four patients were infected with Pseudomonas aeruginosa, 68 with Staphylococcus aureus, and 46 with Haemophilus influenzae, as determined by sputum cultures. The diagnosis of acute pulmonary exacerbation in 39 patients with cystic fibrosis was defined as a marked increase of C reactive protein (median 86 mg/l), by weight loss, anorexia, increased cough, increased sputum production, fever with and without new lung infiltrates, and deterioration of oxygen saturation and pulmonary function. Atopy was present in 31 patients and of these 22 were sensitised against Aspergillus fumigatus. A patient was considered atopic if total serum IgE antibody levels (median total serum IgE 456 ± 22 kU/l, p < 0.0001) were increased (above the age dependent normal values) and if specific IgE antibodies (≥ class 2) against more than one allergen could be detected. None of the patients had received steroids within a month before drawing blood.

Eighty five healthy non-atopic subjects (10.8 (5.68) years) with normal total IgE concentrations (median serum IgE 24 kU/l) were recruited as controls. Blood was obtained at routine sampling for clinical evaluation.

ASSESSMENT OF DISEASE SEVERITY AND PULMONARY FUNCTION

Disease severity was assessed by the Shwachman-Kulczycki score, which in our setting was limited to a maximum of 75 (excluding radiography). The following pulmonary function tests were performed in 67 patients with cystic fibrosis: forced vital capac-
Table 1 Influence of acute pulmonary exacerbation and *P. aeruginosa* infection on serum levels of ECP, MPO, and sIL-2R in 98 patients with cystic fibrosis

<table>
<thead>
<tr>
<th></th>
<th>With (n=39)</th>
<th>Without (n=59)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECP (µg/l)</td>
<td>61.6 (23.4-75.8)</td>
<td>44.9 (14.8-65.0)</td>
<td>NS</td>
</tr>
<tr>
<td>MPO (µg/l)</td>
<td>1342 (1003-1769)</td>
<td>626 (495-804)</td>
<td>&lt;0.0001 &lt;</td>
</tr>
<tr>
<td>sIL-2R (pg/ml)</td>
<td>5040 (4116-7014)</td>
<td>4410 (3570-6804)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Results are presented as median (quartile 1 - quartile 3); p values indicate significant differences between the groups (Mann-Whitney U test). NS = not significant.

Table 2 Correlation (r) of ECP, MPO, and sIL-2R and various clinical parameters

<table>
<thead>
<tr>
<th></th>
<th>ECP</th>
<th>MPO</th>
<th>sIL-2R</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shwachman score</td>
<td>-0.613; p &lt; 0.0001</td>
<td>-0.197; p &lt; 0.005</td>
<td>0.080; NS</td>
</tr>
<tr>
<td>Forced vital capacity</td>
<td>-0.493; p &lt; 0.0001</td>
<td>-0.227; p &lt; 0.01</td>
<td>0.046; NS</td>
</tr>
<tr>
<td>FEV1 (%)</td>
<td>-0.532; p &lt; 0.0001</td>
<td>-0.195; p &lt; 0.05</td>
<td>0.102; NS</td>
</tr>
<tr>
<td>MEF25 (%)</td>
<td>-0.475; p &lt; 0.0001</td>
<td>-0.227; p &lt; 0.01</td>
<td>0.083; NS</td>
</tr>
<tr>
<td>IgG</td>
<td>0.121; NS</td>
<td>0.099; NS</td>
<td>0.009; NS</td>
</tr>
</tbody>
</table>

Correlation was calculated by means of the Kendall Tau B test. NS = not significant.

**Discussion**

Activated neutrophils and eosinophils have been demonstrated to have a deleterious effect on pulmonary tissue in cystic fibrosis.7,11 Neutrophil and eosinophil products together with chronic bacterial infection lead to progressive pulmonary destruction, finally resulting in respiratory failure and death. The role of the neu-
trophiil and its products in cystic fibrosis were elucidated several years ago. These results show a strong relationship between neutrophil activation—that is, MPO concentrations—and pseudomonas infection or acute pulmonary exacerbation. As acute pulmonary exacerbation is generally accepted to be an indication of intravenous antibiotic treatment in cystic fibrosis, the assessment of MPO in peripheral blood may be used as an indicator to start antimicrobial treatment and to monitor the efficacy of the treatment. We have previously shown that antimicrobial treatment reduces serum MPO concentrations which, however, do not return to normal values in patients with cystic fibrosis. This observation thus allows us to hypothesise that, in addition to antibiotic treatment, anti-inflammatory treatment may be indicated in cystic fibrosis.

Raised sIL-2R serum concentrations also indicate anti-inflammatory efforts. In contrast with MPO or ECP concentrations, we did not observe a relationship between sIL-2R and clinical variables. It appears that sIL-2R concentrations show lymphocyte activation and thus explain the excessive immune response in cystic fibrosis. It has been speculated that lymphocyte activity may be an early indicator of a developing inflammatory process in cystic fibrosis and the first sign of airway infection; however, the role of increased sIL-2R concentrations remains to be further investigated.

The role of the activated eosinophil and its products in cystic fibrosis has been investigated previously. The eosinophil is increasingly thought to be a proinflammatory cell in chronic inflammatory respiratory disorders with tissue-damaging capacities. In cystic fibrosis other mechanisms of eosinophil activation than in bronchial asthma should be considered, as in cystic fibrosis eosinophil numbers are within the normal range. We have shown that eosinophils of patients with cystic fibrosis have an increased propensity to release their granule proteins, which may explain the high ECP concentrations in sputum and serum. Eosinophil activity expressed as ECP concentrations was more related to clinical variables such as pulmonary function and the Shwachman-Kulczycki score than were markers of neutrophils and lymphocytes. It has also been shown that mucociliary clearance is decreased in patients with cystic fibrosis who have a normal lung function. It has been suggested that eosinophil products might be responsible for this phenomenon. We were previously able to show that antipseudomonal treatment did not reduce ECP concentrations. These data support the therapeutic recommendation of the use of anti-inflammatory drugs in cystic fibrosis.

In conclusion, the exaggerated inflammatory process in the lungs of patients with cystic fibrosis could be measured in peripheral blood. The assessment of neutrophil activity, measured as MPO concentrations, may be useful in documenting acute pulmonary exacerbations and the infectious status of the patient and to monitor the efficacy of antimicrobial treat-
Inflammatory markers in cystic fibrosis

Concentrations of ECP, a specific marker of eosinophil activation, are strongly related to disease severity in patients with cystic fibrosis and may thus be useful for clinical monitoring in the disease.

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