Serum neopterin as an immunological marker of disease activity in inflammatory diseases
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INCREASED SERUM NEOPTERIN LEVELS IN MYCOSIS FUNGOIDES AND SÉZARY SYNDROME

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PATIENTS AND METHODS
- Patient population
  - Eight patients with mycosis fungoides (MF) and four patients with Sézary syndrome (SS) from the Department of Dermatology University Hospital, Utrecht, and two patients with mycosis fungoides from the Department of Dermatology Academic Medical Centre Amsterdam, were involved in this study.

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Chapter 3

SUMMARY

Neopterin (6-D-erythro-trihydroprolypteridine) is a low-molecular-weight compound derived from guanosine triphosphate. This molecule is synthesized by the macrophage stimulated by interferon-γ. An increased neopterin level is a good reflection of the activation of cellular immunity. It has been suggested that activated macrophages even promote tumor growth. In several malignant diseases, elevated levels of neopterin in urine and serum were observed. Serum neopterin concentration was measured by Radio-Immuno-Assay in patients with mycosis fungoides (n:10) and Sézary syndrome (n:4). Results were compared with those of patients with psoriasis (n:10), atopic dermatitis (n:10) and healthy controls (n:10). Neopterin levels were significantly elevated in patients with mycosis fungoides compared with patients with psoriasis vulgaris, atopic dermatitis and healthy controls (P<0.05). There was no significant difference between Sézary syndrome and psoriasis vulgaris, atopic dermatitis or healthy controls (P>0.05). These findings indicate that serum neopterin concentrations may be a marker of disease activity in mycosis fungoides.

Key words: neopterin mycosis fungoides Sézary syndrome psoriasis vulgaris atopic dermatitis
INTRODUCTION

Neopterin is synthesized in vivo by macrophages from guanosine-triphosphate (GTP) via a series of reactions where the first isolable intermediate 7,8-dihydronopterin-triphosphate has been found. The enzyme GTP-cyclohydrolase-I (EC 3.5.4.16) - catalyzing this reaction - is regulated in a multitude of human and murine cells by cytokines, especially by interferon-γ. Human monocytes/macrophages can be placed in an exceptional position as the activity of the constitutive enzymes is extremely low compared with the interferon-γ dependent GTP-cyclohydrolase-I. Consequently, in monocytes and macrophages instead of synthesizing biopterin, the intermediate 7,8-dihydronopterin-triphosphate is accumulated and after hydrolysis by ubiquitous phosphatases and oxidation it is excreted as 7,8-dihydronopterin or neopterin in blood and urine (1). Evidence for elevated pteridine biosynthesis accompanied with increased neopterin levels can be observed in various diseases which are characterized by the stimulation of the cellular immune system. The latter are viral or bacterial infections (especially intracellular bacteria's) or parasites, autoimmune diseases, certain malignant tumors or allograft rejection (2,3). Thus, the level of neopterin measured in serum and other body fluids allows an inference on the in vivo-activation of the cellular immunity. In one publication elevated levels of neopterin in urine were found in psoriasis patients but not in a heterogeneous group of cutaneous T cell malignancies (4). Activated T lymphocytes have been shown to play a pivotal role in the expression of human immunodeficiency virus in cultures (5) and in patients (6). The purpose of this study is to evaluate the serum neopterin concentration as an additional marker for disease activity in the primary cutaneous T cell lymphomas, mycosis fungoides and Sézary syndrome.

PATIENTS AND METHODS

Patient population
Sera of eight patients with mycosis fungoides (MF) and four patients with the Sézary syndrome (SS) from the Department of Dermatology, University Hospital Utrecht, and two patients with mycosis fungoides from the Department of Dermatology, Academic Medical Centre Amsterdam, were involved in this study. The diagnosis was made on clinical and histological criteria according to the classification of the European Organization for Research and Treatment of
Cancer (EORTC) (7). In this study three patients with MF were included with stage 1a (MF confined to the skin with <10% surface area involved), one patient with stage 1b (MF confined to the skin with >10% surface area involved), four patients with stage 1c (MF confined to the skin with skin tumors), two patients with erythroderma (i.e. mycosis fungoides) and four patients with Sézary syndrome (Table 1).

Table 1. Serum neopterin levels in mycosis fungoides and Sézary syndrome

<table>
<thead>
<tr>
<th>Pat.</th>
<th>m/f</th>
<th>age</th>
<th>stage</th>
<th>present status</th>
<th>serum neopterin level (nmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>m</td>
<td>48</td>
<td>1a</td>
<td>PD</td>
<td>5.5</td>
</tr>
<tr>
<td>2</td>
<td>f</td>
<td>77</td>
<td>1a</td>
<td>PR</td>
<td>6.9</td>
</tr>
<tr>
<td>3</td>
<td>f</td>
<td>72</td>
<td>1a</td>
<td>PR</td>
<td>9.5</td>
</tr>
<tr>
<td>4</td>
<td>m</td>
<td>66</td>
<td>1b</td>
<td>CR</td>
<td>6.9</td>
</tr>
<tr>
<td>5</td>
<td>f</td>
<td>83</td>
<td>1c</td>
<td>D</td>
<td>13.5</td>
</tr>
<tr>
<td>6</td>
<td>m</td>
<td>83</td>
<td>1c</td>
<td>D</td>
<td>17.0</td>
</tr>
<tr>
<td>7</td>
<td>f</td>
<td>75</td>
<td>1c</td>
<td>D</td>
<td>27.4</td>
</tr>
<tr>
<td>8</td>
<td>m</td>
<td>63</td>
<td>1c</td>
<td>D</td>
<td>54.4</td>
</tr>
<tr>
<td>9</td>
<td>m</td>
<td>86</td>
<td>erythrod.</td>
<td>D</td>
<td>13.3</td>
</tr>
<tr>
<td>10</td>
<td>m</td>
<td>84</td>
<td>erythrod.</td>
<td>D</td>
<td>18.9</td>
</tr>
<tr>
<td>11</td>
<td>m</td>
<td>28</td>
<td>SS</td>
<td>D</td>
<td>5.7</td>
</tr>
<tr>
<td>12</td>
<td>m</td>
<td>71</td>
<td>SS</td>
<td>D</td>
<td>6.9</td>
</tr>
<tr>
<td>13</td>
<td>m</td>
<td>60</td>
<td>SS</td>
<td>D</td>
<td>9.8</td>
</tr>
<tr>
<td>14</td>
<td>f</td>
<td>72</td>
<td>SS</td>
<td>D</td>
<td>15.6</td>
</tr>
</tbody>
</table>

Staging classification according to the EORTC (10)

1: mycosis fungoides confined to the skin
   a: limited plaques, papules or eczematous lesions
   b: generalized plaques, papules or eczematous lesions
   c: tumors
PD: progressive disease
PR: partial remission
CR: complete remission
D: died

Control subjects
Sera from 10 untreated patients with mild to severe chronic plaque psoriasis, 10 patients with untreated mild to severe atopic dermatitis and 10 healthy volunteers without skin diseases were used as control sera.
Laboratory investigation:

Neopterin levels in the sera of patients and controls were determined using a commercially available radioimmunoassay kit (Henning, Berlin, FRG). The upper limit of the normal range is approximately 10 nmol/L serum (= 2.5 ng/ml) (8).

RESULTS

Control groups.

Serum neopterin levels of ten patients with psoriasis vulgaris had a range of 3.8-6.8 nmol/L (mean 5.7 nmol/L) and in ten patients with atopic dermatitis the serum neopterin concentration had a range of 2.9-9.9 nmol/L (mean 6.4 nmol/L). In ten healthy volunteers the serum neopterin concentration had a range of 3.8-7.6 nmol/L (mean 5.4 nmol/L). (Table 2)

Table 2. Comparison of serum neopterin levels in nmol/L in patients with Mycosis Fungoides (MF), Sézary syndrome (SS), Healthy Controls (HC), Psoriasis Vulgaris (PV) and Atopic Dermatitis (AD)

<table>
<thead>
<tr>
<th>Pat. Group</th>
<th>N</th>
<th>Range</th>
<th>Mean</th>
<th>SD</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>MF</td>
<td>10</td>
<td>5.5 - 54.4</td>
<td>17.5</td>
<td>14.6</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>SS</td>
<td>4</td>
<td>7.1 - 15.6</td>
<td>9.5</td>
<td>4.3</td>
<td>ns &gt; 0.05</td>
</tr>
<tr>
<td>HC</td>
<td>10</td>
<td>3.8 - 7.6</td>
<td>5.4</td>
<td>1.2</td>
<td>-</td>
</tr>
<tr>
<td>PV</td>
<td>10</td>
<td>3.8 - 6.8</td>
<td>5.7</td>
<td>0.9</td>
<td>-</td>
</tr>
<tr>
<td>AD</td>
<td>10</td>
<td>2.9 - 9.9</td>
<td>6.4</td>
<td>2.4</td>
<td>-</td>
</tr>
</tbody>
</table>

* ANOVA - test

Patients.

In ten patients with mycosis fungoides, six males and four females aged between 48 and 86 years, the serum neopterin concentration had a range of 5.5-54.4 nmol/L (mean 16.3 nmol/L). The three patients with stage 1a and the one patient with stage 1b had serum neopterin concentrations below the upper limit of the normal range, ranging from 5.5 - 9.5 nmol/L. All four patients with stage 1c and the two patients with erythroderma had serum neopterin values above the upper limit of the normal range, ranging from 13.5 - 54.4 nmol/L. (Table 1) One patient with stage 1c was followed during treatment with UV-A in combination with psoralens (PUVA). A serum sample was taken before therapy and eight weeks later during therapy. There was clinically amelioration of the disease and the serum neopterin level dropped from 17.0 nmol/L till 13.0 nmol/L. In four patients
with the Sézary syndrome, the serum neopterin concentration had a range of 5.7-15.6 nmol/L (mean 9.5 nmol/L) (Table 2).

Statistics.
With the One-way analysis of Variance (ANOVA) there was a significant difference between mycosis fungoides in comparison with psoriasis vulgaris, atopic dermatitis and healthy controls (P<0.01). There was not a significant difference between Sézary syndrome in comparison with psoriasis vulgaris, atopic dermatitis and healthy controls (P>0.05) (Table 2).

DISCUSSION
Serum neopterin levels in healthy controls were similar to those found in literature (8). In case of atopic dermatitis serum neopterin concentration was also below the upper limit of the normal range. This was already investigated before in vitro (9). Here the authors suggested that a possible dysregulation of interferon-γ may be related to increased IgE and IgG 4 production. In two studies pretreatment serum neopterin concentrations were not elevated in psoriasis patients and there was no correlation between improvement or deterioration of the psoriasis severity index score (PASI) and the serum neopterin levels (10,11). In contrast other workers showed that fully oxidized urine neopterin levels were significantly elevated in a psoriatic group but not in patients with mycosis fungoides (4). In this latter study there was a strong correlation between the urine neopterin concentration and the PASI score. Urine neopterin and its creatinine ratio were not significantly elevated in patients with mycosis fungoides and there was no correlation with the clinical stage of the disease. However, neopterin levels were elevated in patients with Sézary syndrome. In our study we did not find serum neopterin levels above the upper limit of normal range (< 10 nmol/L) in mild to severe psoriasis patients. An explanation for this contradictory result could be that urine neopterin concentration was determined as opposed to serum neopterin in our study. Although there is a close correlation between serum and urine neopterin levels, urine concentration is one thousand times greater than serum concentration. We found significant elevated levels of serum neopterin in mycosis fungoides as demonstrated in Table 1. This was due to high neopterin levels in stage 1c (n:4) and erythroderma (n:2) but not in
stage Ia (n:3) and 1b (n:1) which demonstrates a correlation between the stage of the disease and the serum neopterin concentration. These results suggest that in the case of a disseminated MF even higher serum neopterin concentrations could be expected. The reason why we did not find elevated neopterin levels in patients with Sézary syndrome (n:4), in contrast to the study mentioned above could be due to the exclusion criteria as e.g. the therapy before serum was taken for the determination of the neopterin concentration. In a previous report it was shown that a high urine neopterin concentration in one patient with mycosis fungoides treated with the immunosuppressant cyclosporine A fell after therapy with a markedly improvement of the clinical condition within eight weeks (12). We observed the same decline of the serum neopterin level with a clinical amelioration of the disease in one patient with mycosis fungoides stage Ic after eight weeks of treatment with PUVA therapy. High levels of serum neopterin in this study demonstrate the role of activated T lymphocytes in patients with mycosis fungoides and support the view that longitudinal studies could be of help in determining the use of neopterin concentrations during therapy, for the identification of relapses and the effect of the therapy. In case of Sézary syndrome, more patients should be evaluated before the start of chemotherapy.

REFERENCES

REFERENCES


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