Coagulation abnormalities in patients with eosinophilia

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Summary: Haematological variables in patients with eosinophilia and in healthy control subjects were studied in order to determine whether there were abnormalities in the coagulation system in patients. We found significantly elevated levels of fibrinogen, fibrin degradation products, platelet number and β-thromboglobulin in patients. The abnormalities were not related to the causes of eosinophilia nor to its severity. This lack of correlation could be due to the heterogeneity of human peripheral blood eosinophils.

Introduction

Thromboembolic disorders are often observed in patients with the hypereosinophilic syndrome (HES)¹ but the causes are unresolved. Eosinophil granule proteins are believed to play two roles in thrombosis: whereas the major basic protein could produce endothelial damage, the cationic protein might produce a hypercoagulable state. However, no previous systematic study of possible coagulation abnormalities has been performed in patients with eosinophilia.

Material and methods

Tests were carried out in 31 patients (15 men) with eosinophilia ranging from $0.9 \times 10^8$ to $7.28 \times 10^9$ cells/l. The causes of eosinophilia in patients were parasitic infection in 9 cases (8 with trichinosis and one with mite itch), vasculitis in 9 cases (including 4 Churg-Strauss syndrome), atopy in 7 cases, solid tumours in 3 cases and lymphoproliferative syndromes in 3 cases. In addition, 50 healthy control subjects (25 men) were studied. The following tests were carried out: (1) Assessment of coagulation pathways by means of prothrombin activity, partial thromboplastin time, and fibrinogen levels. (2) Measurement of fibrinolytic activity by the euglobulins lysis time. Astrup plates and fibrin degradation products (FDP) according to Caen et al.² (3) Platelet count in the peripheral blood using a Hemalog 8/901. (4) Study of platelet function, including platelet aggregation induced by collagen, ADP, ristocetin and arachidonic acid. Platelet adhesivity was studied as reported by Bowie.⁶ Platelet factor 4 (PF4) and β-thromboglobulin (β-TG) levels were measured using RIA with kits from Abbot and Amersham.⁷,⁸ Statistical analysis was performed using Student’s t test and Mann-Whitney U test.

Results

The results are given in Tables I and II. Significant differences were observed between patients and control subjects for fibrinogen levels ($P < 0.001$), platelet number ($P < 0.005$) and β-TG ($P < 0.001$). In addition, the PF4 level tended to be higher in patients than in controls, although that difference was not significant. There was no significant correlation between the severity of eosinophilia and abnormalities in the coagulation tests. Although patients with vasculitis, solid tumours and lymphoproliferative syndromes showed the most marked individual haemostatic abnormalities, there were no significant differences among the various disease groups (Table III).

Discussion

Previous studies on HES indicate a high incidence of associated thrombotic disorders.⁹ Thrombotic and embolic complications have, for example, been observed in ten of fifteen patients with HES.¹ These thrombotic complications have been related to eosinophilia. However, only one of our 31 patients with significant eosinophilia had an arterial thrombosis. No patient showed splinter haemorrhage or retinal lesions. The frequency of coagulation abnormalities in

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Table I  Haematological variables in patients with eosinophilia and in healthy control subjects. The numbers are mean values ± s.d.

<table>
<thead>
<tr>
<th></th>
<th>Prothrombin activity (%)</th>
<th>Partial thromboplastin time (min)</th>
<th>Fibrinogen (mg/100 ml)</th>
<th>Euglobulin lysis time (s)</th>
<th>Astrup plates (mm²)</th>
<th>Fibrin degradation products (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>93.6 ± 12.5</td>
<td>24.5 ± 3.8</td>
<td>404.2 ± 161.4</td>
<td>161.2 ± 52.0</td>
<td>0/132 ± 0/54</td>
<td>17.5 ± 22.3</td>
</tr>
<tr>
<td>Control subjects</td>
<td>89.2 ± 13.2</td>
<td>25.0 ± 3.5</td>
<td>310.5 ± 120*</td>
<td>176.1 ± 60.3</td>
<td>0/142 ± 0/46</td>
<td>5.0 ± 1.2*</td>
</tr>
</tbody>
</table>

* and † indicate significant difference from patients at P < 0.005 and 0.001, respectively.

Table II  Platelet function studies in patients with eosinophilia and healthy control subjects. Numbers shown are mean values ± s.d.

<table>
<thead>
<tr>
<th></th>
<th>Platelet count (10³/mm²)</th>
<th>Platelet adhesivity (%)</th>
<th>Collagen (tsg/ml)</th>
<th>Platelet aggregation (ng/ml)</th>
<th>Ristocetin PF4 (ng/ml)</th>
<th>β-TG (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>320 ± 124</td>
<td>26.0 ± 18.0</td>
<td>71.9 ± 38.3</td>
<td>65.8 ± 28.9</td>
<td>81.9 ± 32.6</td>
<td>76.5 ± 59.3</td>
</tr>
<tr>
<td>Control subjects</td>
<td>236 ± 106*</td>
<td>23.5 ± 15.2</td>
<td>67.3 ± 14.3</td>
<td>57.4 ± 14.4</td>
<td>80.0 ± 10.0</td>
<td>31.0 ± 12.0*</td>
</tr>
</tbody>
</table>

* and † indicate significant difference from patients at P < 0.005 and 0.001, respectively

Table III  Haematological parameters in various eosinophilic diseases

<table>
<thead>
<tr>
<th>Disease group</th>
<th>Fibrinogen (mg/100 ml)</th>
<th>Fibrin degradation products (µg/ml)</th>
<th>Platelet count (10³/mm²)</th>
<th>PF4 (µg/ml)</th>
<th>β-TG (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parasitic infection (n = 9)</td>
<td>425 ± 117*</td>
<td>7.7 ± 8.3*</td>
<td>311 ± 94.7</td>
<td>17.4 ± 25.9</td>
<td>72 ± 57</td>
</tr>
<tr>
<td>Atopia (n = 7)</td>
<td>365 ± 136</td>
<td>25 ± 13.8*</td>
<td>288 ± 74.6</td>
<td>10.4 ± 8</td>
<td>82.6 ± 65</td>
</tr>
<tr>
<td>Vasculitis (n = 9)</td>
<td>361 ± 122</td>
<td>21 ± 37.9*</td>
<td>318 ± 170.8</td>
<td>7.8 ± 9.6</td>
<td>50.3 ± 22.8</td>
</tr>
<tr>
<td>Solid tumours (n = 3)</td>
<td>646 ± 299</td>
<td>15 ± 13.2*</td>
<td>354 ± 221.9</td>
<td>7.5 ± 6.4</td>
<td>83 ± 50.4</td>
</tr>
<tr>
<td>Lymphoproliferative syndromes (n = 3)</td>
<td>381 ± 142</td>
<td>21.7 ± 14.4*</td>
<td>407 ± 42.5*</td>
<td>53 ± 75.3</td>
<td>163 ± 96.4</td>
</tr>
<tr>
<td>Control subjects</td>
<td>310 ± 120</td>
<td>5 ± 1.2*</td>
<td>263 ± 106</td>
<td>5 ± 3</td>
<td>31 ± 12</td>
</tr>
</tbody>
</table>

* indicates significant difference from healthy adult controls at P < 0.05.

our study was relatively low, and was probably related mainly to platelet activation, since thrombocytosis can be reactive and fibrinogen elevated due to its character as acute phase reactant.

The increase in FDP is most likely due to a fibrinolytic reaction that occurs as a result of formation of fibrin, as is seen in some inflammatory processes. Although we did not find signs of either disseminated intravascular coagulation or a hypercoagulable state, we can not rule out that cationic protein mediated activation of the intrinsic pathway through the Hageman factor, as a possible cause of the abnormalities observed in the coagulation system in our patients.

The most constant findings in our study were an increase in PF4 and β-TG, both being indirect signs of platelet activation. The rise in β-TG was more marked and constant than the rise in PF4, perhaps due to the fact that β-TG is a stable metabolite of PF4 (half-lives of 100 minutes and 10 minutes, respectively). Several factors, acting alone or together, may account for the platelet hyperactivation observed in our patients with eosinophilia. One factor is endothelial damage related to major basic protein. Increased biosynthesis of platelet activating factor (PAF) in activated human eosinophils could also be involved in the pathogenesis; the generation of PAF could be secondary to activation of eosinophilic chemotactic factor. Another possible factor is injury to the endothelium caused by circulating Charcot...
Leyden crystals which might also contribute to the pathogenesis. Clearly, a combination of effects of these factors could lead to vascular damage in eosinophilia.

The absence of any correlation between the severity of the eosinophilia and the different coagulation parameters, such as PF4 and β-TG levels, might be due to the heterogeneity of the human peripheral blood eosinophils, and specifically, to the mechanisms of eosinophil degranulation. The lack of differences among different groups of diseases can be attributed to this same mechanism or to the small number of patients in each group.

Acknowledgement

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References

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