Serum Immunoglobulin E in Pemphigus

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Immunoglobulin E levels in the sera of patients with pemphigus (12 with Brazilian pemphigus foliaceus (BPF) and 11 with pemphigus vulgaris (PV)) were determined by means of a solid phase radioimmunoassay. A significant increase in IgE level was observed in BPF patients compared to the level of IgE in PV patients and healthy adults. The implications of an elevated level of IgE with respect to other aberrations of immunologic responsiveness and the suggested infectious etiology of BPF are considered.

Numerous studies have confirmed the association of elevated levels of serum immunoglobulin (Ig) E and diseases of parasitic etiology [1]. Epidemiologic studies of Brazilian pemphigus foliaceus (BPF) have suggested an infectious etiology [2]. This suspect etiology and unexplained elevations of the third component of complement (C3) in the serum of patients with pemphigus (BPF and pemphigus vulgaris [PV]) [3] may possibly be attributable to one or more factors affecting the activation of C. These include activation of: (i) the classical C pathway by circulating and locally produced immune complexes [4] and/or (ii) the alternative C pathway by aggregated IgE [5]. Alternatively, but not mutually exclusive, is activation of the alternative C pathway by (i) the infectious agent in BPF or (ii) the lipoidal epithelial antigen of pemphigus [6,7] itself.

In an initial inquiry of the above possibilities, the levels of IgE and their pathophysiologic association in patients with pemphigus have been evaluated.

MATERIALS AND METHODS

Patients

Thirty patients with pemphigus (19 with BPF and 11 with PV) were evaluated. The diagnosis of pemphigus was established by clinical and histological examination by the patient's attending physician and by demonstration of antibodies to the intercellular (IC) areas of stratified squamous epithelium by indirect IF [8].

Based on the presence and extent of skin or mucous membrane lesions, disease activity in these patients was in the moderate to severe category [9]. Immunofluorescent staining titres for IC antibodies ranged from 1:640 to 1:500 in patients with BPF and from 1:80 to 1:640 in patients with PV as determined by one of us (RJA).

Serum Specimens

Serum was obtained from each patient prior to treatment when possible, or following minimal therapy with corticosteroids.*

Serum from 9 healthy adults without any apparent clinical evidence of disease or allergy served as controls. All sera were stored at −20°C until use.

Determination of Serum IgE

The level of circulating IgE was determined by solid phase radioimmunoassay employing the Phadebas IgE Test Kit (Pharmacia Ltd., Upsala, Sweden). This method employs an insolubilized anti-IgE antibody and the competitive inhibition of its binding to 125I-labeled IgE [10]. The standards employed were calibrated against IgE, 68/341 from the WHO International Reference Centre (Lausanne, Switzerland). Levels of IgE were given in U/ml.

For IgE determinations, all serum specimens were initially diluted tenfold with buffer. When required for accuracy at high concentrations, specimens were appropriately diluted until concentrations within the range of 1–400 U/ml were achieved. The concentration was then multiplied by the dilution factor.

Elimination of possible falsely elevated IgE levels due to the presence of nonspecific blocking factors in the serum of the patients evaluated was taken into account by multiplying the mean count-rate by 0.96, the ratio between zero samples consisting of buffer and IgE-free serum [10].

Statistical Analysis

The significance of the level of IgE, that is, the probability (P) that the difference between the mean serum concentration of IgE for patients with BPF and PV to that of IgE in healthy adults and that of BPF vs. PV patients was due to chance, was determined by the Student's t-test of paired variables [11].

RESULTS AND DISCUSSION

The distribution, range and mean ± SD of levels of serum IgE determined by solid phase radioimmunoassay in 19 patients with BPF and 11 patients with PV and the significance of the level between each and in comparison with levels of IgE in healthy adults are shown in the Table. As shown in the Table, significantly (P < 0.01) elevated levels of serum IgE were observed in BPF patients compared to the levels of IgE in PV patients and healthy adults. Particularly striking were the inordinately elevated levels in BPF patients: 12 (63%) had levels >10,000 U/ml; 6 (32%) having levels >20,000 U/ml and 2 (11%) patients with a level >30,000 U/ml.

By comparison, only 3 (27%) patients with PV vs. 19 (100%) with BPF had levels >300 U/ml. One PV patient had a level of IgE of 700 U/ml and 2 had levels of 1250 and 1598 U/ml, respectively.

None of the healthy adults had levels >300 U/ml.

It will be noted from the range and mean ± SD shown in the Table, that there was a large variation in the level of IgE in the healthy adults employed as controls. However, it is believed that as these levels fall within the lower and upper limits of normal for normal circulating levels of IgE [12], that this did not influence, significantly, interpretation of the data in this study.

The virtual absence of elevated levels of IgE in PV patients evaluated in this study is in agreement with previous quantitation of serum IgE by single radial radioimmunodiffusion [13]. However, elevations of IgE in BPF and their frequency compared with those in PV point to the possible importance of several of the pathophysiologic manifestations involving IgE as contributory to the cutaneous lesions in BPF possibly not operative in PV.

* BPF patients courtesy of Prof. Dr. Otto Bier, Servico de pénigo foliacé Sao Paulo, Brazil and PV patients courtesy of Prof. Ernst H. Beutner, Department of Microbiology, State University of New York at Buffalo School of Medicine, Buffalo, New York.
### Distribution of serum IgE levels in patients with Brazilian pemphigus foliaceus and pemphigus vulgaris

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. patients</th>
<th>Level of immunoglobin E (U/ml)</th>
<th>Range</th>
<th>Mean ± SD</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brazilian pemphigus foliaceus</td>
<td>19</td>
<td>&lt;300  300-900  900-1500  &gt;1500</td>
<td>1450–&gt;30,000</td>
<td>13,096.3 ± 8676.7&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Healthy adults</td>
<td>9</td>
<td>0     0     1     18</td>
<td>5–160</td>
<td>75.0 ± 50.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Pemphigus vulgaris</td>
<td>11</td>
<td>8     1     0     2</td>
<td>&lt;1–1598</td>
<td>372.5 ± 588.6&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&lt;0.40</td>
</tr>
</tbody>
</table>

<sup>a</sup> Excluding 2 patients with levels >30,000 U/ml.
<sup>b</sup> Excluding 1 patient with level <1 U/ml.

The clinical significance of elevated levels of IgE in BPF and its possible antigenic specificity are not known and cannot be determined from the present data. Accumulating evidence suggests that an IgE response may be attributed to infectious agents but with varying results for the host, e.g., an IgE antibody may facilitate control of infection as in the case of the rodent's response to nematodal infection [14] or the participation of IgE in an immune response may be detrimental, contributing to exacerbation of disease as in the development of immune complex disease in the rabbit [15].

In light of the association of elevated levels of IgE and diseases of parasitic etiology [1], elevation of IgE in BPF may be reflective of its earlier suggested infectious etiology [2], in which the insect, commonly known as Burasibius, has been implicated in one of the principle foci in Brazil where BPF is endemic.

Elevation of IgE in BPF may also offer some explanation, among other possibilities mentioned initially, of earlier observations of elevated levels of C3 in BPF [3] due to activation of the alternative C pathway via aggregated IgE [5]. However, cursory inquiry of this suggested relationship between levels of IgE and C3 in the patients evaluated in this study disclosed that there was no obvious relationship between these 2 variables (Ablin, unpublished observations).

Absence of this initially thought relationship has prompted evaluation, among other alternatives, but not mutually exclusive explanations for elevations of C3, of activation of the alternative C pathway by the lipoidal epithelial antigen of pemphigus [6,7], which is presently under investigation.

### REFERENCES

### Annual Hair Transplant Symposium and Workshop

The Annual Hair Transplant Symposium and Workshop will be held in Hot Springs, Arkansas, U.S.A., January 25–28, 1979. The registration fee is $720. Inquiries can be made to D. B. Stough, III, M.D., Program Chairman, Stought Dermatology and Cutaneous Surgery Clinic, P. A., Doctors Park, Hot Springs, Arkansas 71901.