Hyposplenism, adult coeliac disease, and autoimmunity

ALICE W BULLEN,* R HALL, G GOWLAND, S RAJAH, AND M S LOSOWSKY†

From the University Department of Medicine, St. James's Hospital, Leeds, the University Department of Immunology, The General Infirmary, Leeds, and the Regional Blood Transfusion Service, Leeds

SUMMARY Functional hyposplenism is associated with a variety of disorders including coeliac disease. The aims of this study were to estimate the need for a small intestinal biopsy in the investigation of hyposplenism, and to assess the relationship of autoimmunity to hyposplenism and coeliac disease. During one year, the features of hyposplenism were found in blood films of 27 patients who had not had a splenectomy. Ten patients were already known to have coeliac disease. Intestinal biopsy was performed in another 13 patients; coeliac disease was diagnosed in six. Of the 23 patients biopsied, coeliac disease was present in 16 (70%). Autoantibodies were detected in significantly more patients with hyposplenism than in healthy controls (p <0.05), and in significantly more coeliacs with hyposplenism than coeliacs with normal blood films (p <0.01). The increased incidence of autoantibodies in coeliacs with hyposplenism compared with other coeliacs was not associated with a difference in the incidence of HLA-B8. Small bowel biopsy should be carried out in the investigation of unexplained hyposplenism. There may be a link between hyposplenism and the autoimmune manifestations of coeliac disease.

1 Disease associated with blood film evidence of hyposplenism

It has been suggested that the diagnosis of coeliac disease should be seriously considered in any patient found to have evidence of unexplained hyposplenism in a blood film.1 However, a wide variety of disorders other than coeliac disease may be associated with functional asplenia,2–4 including a spectrum of conditions associated with autoimmunity.5 Known associations with hyposplenism include dermatitis herpetiformis, inflammatory bowel disease (ulcerative colitis, and, less commonly, Crohn's disease), sickle cell disease, systemic lupus erythematosus, rheumatoid arthritis, thyroid disorders, splenic artery or vein occlusion, thrombocytopenia, conditions causing infiltration or replacement of splenic tissue—for example, amyloid, lymphoma, previous Thorotrast administration, and congenital asplenia.

We have investigated all patients found to have features of hyposplenism by examination of blood films in the Haematology Department of a general hospital during a period of one year. When a patient had not had a previous splenectomy, consideration was given to the underlying diagnosis, the result of a small intestinal biopsy, and evidence of autoimmunity. The aims of the study were to estimate the need for a small intestinal biopsy in the investigation of hyposplenism and to assess the incidence of autoimmunity in patients with hyposplenism and in control subjects.

Methods

Patients

Over a period of one year, approximately 40 000 routine blood films were scrutinised for the presence of the features of hyposplenism—that is, Howell Jolly bodies, acanthocytes, giant platelets, and target cells. Fifty-eight patients were found to have blood film evidence of hyposplenism, and of these 31 had had a previous splenectomy, leaving 27 patients with presumed functional hyposplenism. These 27 patients were additionally investigated by full clinical examination and inspection of case records, to establish the underlying diagnosis and obtain any clinical evidence of autoimmune disease. Multiple small intestinal biopsies with the Quinton hydraulic capsule were obtained in 23 patients. Confirmatory evidence of hyposplenism was obtained (by heat-damaged red cell clearance studies, spleen...
Hyposplenism and autoimmunity

Table 1  Autoantibodies detected, tissue type, and result of intestinal biopsy in 27 patients with blood film evidence of hyposplenism who had not had a splenectomy

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (yr) and sex</th>
<th>Diagnosis</th>
<th>GPC</th>
<th>SMA</th>
<th>ANA</th>
<th>AMA</th>
<th>TMA</th>
<th>TCAT</th>
<th>RF</th>
<th>Retic</th>
<th>HLA-B8</th>
<th>Intestinal biopsy</th>
<th>Hyposplenism confirmed by spleen scan and/or red cell clearance</th>
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<td>46F</td>
<td>CD Hypothyroid, Ca uterus</td>
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<td>+</td>
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<td>+</td>
<td>+</td>
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<td>58F</td>
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<td>+</td>
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</tbody>
</table>

+ = positive test. --- = negative test. ND = not done. GPC: gastric parietal cell antibody; SMA: smooth muscle antibody; ANA: nuclear antibody; AMA: mitochondrial antibody; TMA: thyroid microsomal antibody; TCAT: thyroglobulin antibody; RF: rheumatoid factor; retic: reticulin antibody.

Results

The results in the 27 patients with hyposplenism are shown in Table 1. Ten patients were already known to have coeliac disease and were on a gluten free diet. Six patients were subsequently submitted to biopsy and found to have coeliac disease, with improvement of the biopsy on a gluten free diet. In three of these patients there were obvious reasons for performing a biopsy apart from the finding of hyposplenism. In the other three patients, the finding of hyposplenism was the major reason for performing the biopsy, although there were other features, such as a past history of anaemia, which contributed to the decision. In four patients, all 75 or more years old, a small bowel biopsy was not considered to be justified. Two of these patients, one with dermatitis herpetiformis and one with malabsorption, anaemia,
and multiple nutritional deficiencies, may well have had a mucosal lesion. The other two patients had no obvious explanation for hyposplenicism; although spleen weight decreases with age, it is not clear whether this can be severe enough to cause blood film changes.

Seven patients were submitted to biopsy and found not to have coeliac disease. In five of these patients there was a past history of diarrhoea or recurrent anaemia. The patients with dermatitis herpetiformis and IgA deficiency had slightly raised interepithelial lymphocyte counts in otherwise normal biopsies. The patient with hereditary thrombocytopenia had a markedly raised eosinophil count in an otherwise normal biopsy. Biopsies in the patients with thyroid disease, severe asthma and eczema, and pyelonephritis with congenital urinary tract abnormality were normal.

Of 23 patients with hyposplenicism who had had an intestinal biopsy, coeliac disease was present in 16 (70%).

In six out of 27 patients (22%) hyposplenicism was associated with clinical autoimmune disease (Table 1). Four patients had thyroid disorders, one insulin dependent diabetes mellitus, and one pernicious anaemia. Four out of the 27 had some form of malignancy (15%).

The types of autoantibodies detected in the patients with hyposplenicism and in seven out of 27 age and sex-matched healthy controls are shown in Tables 1 and 2. Of the 27 patients with hyposplenicism, 16 had one or more autoantibodies (59%); five patients had more than one antibody, and one patient had reticulin antibody only. Of the 27 controls, seven had autoantibodies (26%); one subject had two antibodies and one had reticulin antibody only. Autoantibodies were detected in a significantly higher number of patients with hyposplenicism than in controls (p < 0.05, χ² test). If patients with reticulin antibody only are excluded, because of the possibility that this is a food antibody rather than an autoantibody, these differences remain significant, suggesting that autoantibodies are more common in patients with hyposplenicism than in age and sex-matched controls.

**Discussion**

The results suggest that coeliac disease is the commonest cause of hyposplenicism found on blood film screening in a general hospital, and therefore support the suggestion that small bowel biopsy should be seriously considered in subsequent investigation. It is perhaps surprising that we found no patients with hyposplenic blood films in association with ulcerative colitis. This is probably due to chance, and because relatively few patients with severe colitis, in whom hyposplenic blood films are more likely to be found, were seen during the period of study. However, such patients usually have marked symptoms and a previous history of colitis, so that the cause of hyposplenicism is easily suspected. Of our seven non-coeliacs with hyposplenicism, three had diseases known to be associated with splenic atrophy—that is, thyroid disorders and dermatitis herpetiformis. The patient with hereditary thrombocytopenia may have had a vascular cause for hyposplenicism. The patient with a congenital abnormality of the urinary tract may have had associated congenital asplenia, although this is very rare without a heart lesion. To our knowledge, hyposplenicism has not been previously described in association with IgA deficiency, or with severe asthma and eczema, both diseases with disturbance of immunity.

We have found a high incidence of autoimmunity in association with hyposplenicism, confirming the findings of Wardrop et al. However, as coeliac disease was known to be present in 16 out of our 23 biopsied patients with hyposplenicism, and thought to be present in eight out of the 14 cases described by Wardrop et al., the high incidence of autoimmunity might be related to the predominance of coeliacs in the two groups, rather than to splenic atrophy per se. Although autoimmune diseases may be associated with splenic atrophy in the absence of coeliac disease, we believe that the finding of autoimmune disease cannot be considered to be the explanation for splenic atrophy in an individual patient unless coeliac disease has been excluded, as the three conditions may coexist. This was the case in our patients and those described by others—for example, coeliac disease and splenic atrophy associated with rheumatoid arthritis, thyrotoxicosis, or primary biliary cirrhosis. It is not clear whether autoimmune disease precedes and causes splenic atrophy, or vice versa, or whether an additional factor—for example, HLA status—influences both conditions.

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**Table 2**  Autoantibodies detected in seven out of 27 healthy control subjects matched for age and sex with the patients with hyposplenicism

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<tr>
<th>Subject no.</th>
<th>GPC</th>
<th>SMA</th>
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<th>AMA</th>
<th>TMA</th>
<th>TCAT</th>
<th>RF</th>
<th>Retic</th>
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*Bullen, Hall, Gowland, Rajah, and Losowsky*
Hyposplenism and autoimmunity

2 Association between adult coeliac disease, hyposplenism, and autoimmunity

The results described above suggest that coeliac disease is a common cause of unexplained hyposplenism, and that hyposplenism is commonly associated with autoimmunity. However, coeliac disease itself is known to be associated with an increased incidence of autoimmunity. The relationship of hyposplenism to autoimmunity in coeliac disease has not been fully assessed.

We have compared 16 treated coeliacs with hyposplenism with 29 treated coeliacs with normal blood films. The aim of the study was to assess the incidence of autoimmunity with and without hyposplenism. As certain autoimmune diseases are associated with HLA-B8, which is also commonly associated with coeliac disease, the results have been related to HLA type.

Methods

Patients

Sixteen treated coeliacs (mean age 51 years, range 37–62 years) with the blood film features of hyposplenism, and 29 treated coeliacs (mean age 41 years, range 16–70 years) with normal blood films were examined for clinical evidence of autoimmune disease, and serum was screened for autoantibodies as described above. Fifteen of the coeliacs with hyposplenism and 25 of the coeliacs with normal blood films were tissue types for 24 HLA-A and B antigens using the NIH technique. All patients gave informed consent to the investigation.

Results

Four out of 16 coeliacs with hyposplenism had clinical autoimmune disease (Table 1). One of the control group of 29 coeliacs with normal blood films had an autoimmune disease (hyperthyroidism). The incidence of clinical autoimmune disease in the coeliacs with hyposplenism is significantly greater than in those with normal blood films (p = 0.047, Fisher’s exact test). This suggests that clinical autoimmune disease is found more frequently in association with hyposplenism than in coeliac disease alone, but the numbers are small and, furthermore, the mean age of the coeliacs with normal blood films was lower than in those with hyposplenism. Those with hyposplenism were then compared with age and sex-matched coeliacs with normal blood films, of whom one out of 16 had an autoimmune disease; although it is suggestive, this difference in incidence is not significant, but a larger series would be needed to assess significance more authoritatively. Interestingly, three of the 16 coeliacs with hyposplenism had some form of malignancy, whereas none of the coeliacs with normal blood films had malignancy.

Autoantibodies were detected in 11 out of 16 treated coeliacs with hyposplenism (69%); three patients had more than one antibody and one patient had reticulin antibody only (Table 1). Autoantibodies were detected in six out of 29 treated coeliacs with normal blood films (21%); one patient had two autoantibodies and one patient had reticulin antibody only (Table 3). Autoantibodies were detected in significantly more coeliacs with hyposplenism than in coeliacs with normal blood films (p < 0.01, x² test). If the coeliacs with hyposplenism were compared with age and sex-matched coeliacs with normal blood films, of whom four out of 16 had autoantibodies, the difference is still significant (p < 0.05, x² test), and remains so if patients with reticulin antibody only are excluded. This suggests that autoantibodies are more common

Table 3 Autoantibodies detected in six out of 29 patients with treated coeliac disease and normal blood films

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<th>TMA</th>
<th>TCAT</th>
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</table>

Table 4 Incidence of HLA-B8 in coeliac patients with and without hyposplenism and with and without autoantibodies

<table>
<thead>
<tr>
<th></th>
<th>No. tissue typed</th>
<th>B8+ (no.) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coeliacs with hyposplenism</td>
<td>15</td>
<td>11</td>
</tr>
<tr>
<td>Coeliacs without hyposplenism</td>
<td>25</td>
<td>18</td>
</tr>
<tr>
<td>Coeliacs with autoantibodies</td>
<td>16</td>
<td>11</td>
</tr>
<tr>
<td>Coeliacs without autoantibodies</td>
<td>24</td>
<td>18</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>No. tissue typed</th>
<th>With antibodies (no.) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA B8+ ve coeliacs</td>
<td>29</td>
<td>11</td>
</tr>
<tr>
<td>HLA B8-ve coeliacs</td>
<td>11</td>
<td>45 NS</td>
</tr>
</tbody>
</table>
in patients with coeliac disease and hyposplenism
than in other coeliac patients.

In order to determine whether the higher incidence
of autoantibodies in coeliacs with hyposplenism is
related to a higher incidence of HLA-B8, the inci-
dence of HLA-B8 was compared in coeliac patients
with and without hyposplenism and with and without
autoantibodies (Table 4). There was no significant
difference in the incidence of HLA-B8 in each group.
There was no significant difference in incidence of
autoantibodies between the HLA-B8 positive and
HLA-B8 negative coeliacs.

Discussion

Autoantibodies occur more frequently in coeliacs
with hyposplenism than in those with normal blood
films. This does not appear to be related to a differing
incidence of HLA-B8 in those with or without hypo-
splenism or with and without autoantibodies. Kumar et al.34
have also found that the presence of autoantibodies
does not differ significantly in HLA-B8 positive and B8-negative coeliacs.

The incidence of autoantibodies increases with
age, and the incidence of hyposplenism in coeliacs
also increases with age at starting a gluten-free
diet.25 However, if coeliacs are matched for age and
sex, the incidence of autoantibodies remains greater
in association with hyposplenism. We therefore
suggest that there may be a link between the auto-
immune manifestations of coeliac disease and the
defect in splenic function.

The nature of this link is not known. It has been
suggested28 that some immunological disorders
associated with coeliac disease occur as a result of
circulating immune complexes originating in the
damaged small intestine. Splenic atrophy might also
occur as a result of prolonged uptake of immune
complexes; decreased splenic function has been
found in association with circulating immune com-
plexes, and this can be reversed by plasma ex-
change.27 28 The incidence of circulating immune
complexes in coeliac disease is disputed,29 but it is
thought to be less after treatment.30 However,
treatment of coeliac disease does not prevent the
onset of immunological disorders;18 one of our
patients developed myxoedema 14 months after
starting a gluten free diet. It is possible that the
splenic atrophy develops because of prolonged
immune complex uptake or some other mechanism,
such as prolonged lymphocyte loss31 while the
patient is untreated, and the splenic atrophy then
predisposes to autoimmune disease, which may
occur after the patient is treated. Although there is a
reversible component to splenic hyphofunction in
some patients,22 in the majority of our coeliacs with
hyposplenism it is present after prolonged treat-
ment.25 33 Splenic hyphofunction may be associated
with alteration of lymphocyte production34 and
lymphocyte subpopulations in the peripheral blood.35
It has been shown that the spleen is a major source
of suppressor cells;35–37 these cells are thought to be
important in the regulation of autoimmunity38–40
and it is possible that, in coeliac disease with hypo-
splenism, suppressor cells are decreased or abnormal.

Although the numbers of patients are small, the
incidence of malignant disease in those with hypo-
splenism is greater than in those with a normal blood
film, and this might warrant study in a larger series.

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Hyposplenism, adult coeliac disease, and autoimmunity.

A W Bullen, R Hall, G Gowland, S Rajah and M S Losowsky

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