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Coeliac disease, splenic function, and malignancy

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SUMMARY Blood films from 41 cases of coeliac disease complicated by malignancy were examined and evidence of hyposplenism found in 12 cases (29%). This is similar to the proportion of adult coeliacs without malignancy who have hypoplenism and it is concluded that impaired splenic function is not associated with the development of malignancy in coeliac disease.

Malignancy is a well-recognised complication of coeliac disease,[1 2] the characteristic tumour being small intestinal lymphoma,[3] but increased susceptibility to other malignancies, particularly of the gastrointestinal tract, is also recognised.[4] Why patients with coeliac disease should develop malignancy is unknown. Villous atrophy may be a pre-malignant condition, chronic nutritional deficiency[5] or uptake of a carcinogen from the gastrointestinal tract may lead to malignant change, or there may be inadequate immune surveillance in the coeliac patient.

Immune abnormalities occur frequently in coeliac disease. Autoantibodies and autoimmune disease are common,[6] and atrophy of the lymphoreticular system, in particular the spleen, is well recognised.[7] The mechanism of splenic atrophy remains unknown. It may be a complication of chronic folate deficiency, or may be the result of excessive loss of lymphocytes through the damaged gastrointestinal tract, and there are animal models to support both these hypotheses.[8 9] Alternatively, splenic atrophy may occur as a result of the same immunological damage that causes the villous atrophy.

It has been suggested that splenic atrophy and malignant disease may be related[7] – for example, as well as causing splenic atrophy, loss of lymphocytes through the gastrointestinal tract may lead to loss of cell-mediated immunity and immune surveillance and the development of neoplasia. In support of this, lymphoma of the small bowel has been associated with the lymphocyte depletion occurring in intestinal lymphangiectasia.[10] Splenic atrophy was noted in four out of 10 coeliacs with malignancy in Thompson's post-mortem study,[3] and malignancy was noted in three out of 16 coeliacs with splenic atrophy in the series[11] of Bullen *et al.* No excess mortality from malignant disease was noted, however, in the study of veterans of the second world war who underwent splenectomy for trauma, although mortality from other causes was increased.[12]

To assess whether splenic atrophy is associated with malignancy in coeliac disease we have looked for blood film evidence of hyposplenism in coeliac disease complicated by malignancy.

Methods

PATIENTS

Unstained blood films were obtained from 41 patients, reported to the National Study of Coeliac Disease and Malignancy (which will be reported in full elsewhere) to have histologically confirmed coeliac disease and histologically diagnosed malignancies, who were available for study, and from whom blood samples could be readily obtained. The films were fixed in methanol at the reporting centre and sent to Leeds where they were stained and examined. Diagnostic features noted were Howell-Jolly bodies, target cells, acanthocytes, and giant platelets, which we have shown to correlate well with more sophisticated tests of splenic function. If two or more of these abnormalities were present in the absence of any other possible cause for them on the blood film, hyposplenism was diagnosed.

Results

Clinical features of the 41 patients and results of blood film analysis are shown in the Table.

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Table *Clinical data of 41 patients with coeliac disease complicated by malignancy*

Patient no.	*Sex*	*Age (yr) at diagnosis of coeliac disease*	*Duration of GFD before diagnosis of malignancy (yr)*	*Malignancy*		*Blood film evidence of hyposplenism*
				Type	*Site*	
1	M	59	0	Adenocarcinoma	Caecum	−
2	F	57	0 (1)	Squamous	Tongue	−
			10 (2)	Squamous	Bronchus	
3	M	54	1	PRV		−
4	M	66	0	Lymphoma	Small bowel	−
5	F	53	16	Glioma	Brain	−
6	M	56	1 (1)	Squamous	Bronchus	+
			5 (2)	Squamous	Ear	
7	M	42	0	Adenocarcinoma	Stomach	−
8	M	46	5	Lymphoma	Abdominal nodes	−
9	M	64	0	Lymphoma	Small bowel	−
10	M	49	0	Lymphoma	Small bowel	+
11	F	58	9	Lymphoma	Lymph nodes	−
12	F	35	1	Adenocarcinoma	Disseminated	−
13	F	48	4	Somatostatinoma	Pancreatico-duodenal region	−
14	F	67	6	Lymphoma	Groin nodes	+
15	M	48	11	Adenocarcinoma	Stomach	+
16	F	57	7	Squamous	Oesophagus	+
17	M	39	0	Seminoma	Testis	−
18	M	53	0	Lymphoma (1)	Small bowel	−
			0	Undifferentiated (2) Carcinoma	Bronchus	
19	M	68	1	Squamous	Bronchus	+
20	M	52	9	Lymphoma	Small bowel	−
21	M	46	1	Lymphoma	Small bowel	+
22	F	46	8	Adenocarcinoma	Ampulla of Vater	+
23	M	53	0	Adenocarcinoma	Rectum	−
24	M	38	0	Teratoma	Testis	−
25	M	35	0	Teratoma	Testis	−
26	F	49	0	Lymphoma	Small bowel/liver	−
27	M	63	0	Lymphoma (1)	Small bowel	
				Basal cell carcinoma (2)	Nose	
				Adenocarcinoma (3)	Small bowel	
28	F	71	0	Lymphoma	Small bowel	−
29	M	39	0	Lymphoma	Thyroid	−
30	M	64	0	Adenocarcinoma	Small bowel	+
31	F	39	0	Acute lymphocytic leukemia		−
32	F	54	0	Adenocarcinoma	Breast	−
33	F	61	0	Myeloma		−
34	F	55	6	Lymphoma	Small bowel	−
35	M	57	0	Lymphoma	Principally, abdominal lymph nodes	−
36	F	42	0	Lymphoma	Small bowel	+
37	M	68	3	Lymphoma	Stomach	+
38	F	52	0	Adenocarcinoma	Duodenum	−
39	M	42	4	Adenocarcinoma	Small bowel	−
40	M	62	0	Lymphoma	Small bowel	−
41	F	68	0	Lymphoma	Small bowel	+

GFD: gluten free diet.
PRV: polycythaemia rubra vera

Twelve patients (29%) were considered to have blood film changes diagnostic of hyposplenism. Of these, seven had all four blood film abnormalities, three had three, and two had two only. Two patients had target cells and giant platelets, which might not have been due to hyposplenism: patient 3 had polycythaemia rubra vera, and patient 8 a regenerating hypochromic anaemia, and these were considered not to have hyposplenism.

If the group with hyposplenism is compared with the remainder, they are seen to be older at the time of diagnosis of coeliac disease (57 v 51 years) and at the time of blood film examination (63 v 57 years), but these differences were not statistically

significant. Similar proportions in each group developed lymphoma at any site (6/12 v 13/29) and small intestinal tumours (6/12 v 12/29). Of the four individuals with more than one tumour, only one had hyposplenism.

Discussion

Splenic size and function has been measured in coeliac disease using a variety of methods of differing sensitivity. These methods include measuring the rate of clearance of heat-damaged red cells from the circulation, a measure of reticulo-endothelial function,[13] visualisation of the spleen by scintography[14] when the volume of functioning splentic tissue can be calculated, and evidence of impaired splenic function on the blood film.[15] Splenic function in coeliac disease probably declines gradually until there may be a slightly reduced splenic volume, with slightly delayed red cell clearance, although the spleen still retains enough function to clear inclusions such as Howell-Jolly bodies from red cells. It follows that the reported incidence of hyposplenism depends upon the method of detection, and upon the age of the patient, particularly the age at which a gluten-free diet was instituted.

Thus Pettit *et al*[16] found in their study of patients with dermatitis herpetiformis associated with small bowel biopsy abnormalities that seven of 24 patients (mean age 46 years) had evidence on blood film of hyposplenism, eight had delayed red cell clearance, and that the average spleen size was well below the normal mean, but still within the normal range.

Marsh and Stewart[17] found that five of 18 patients (mean age 51 years) with adult coeliac disease had evidence on blood film of hyposplenism, and that these five patients had marked delay in clearance of heat-damaged red cells. Nine other patients had slightly delayed clearance, but normal blood films. McCarthy *et al*[7] found evidence of splenic atrophy in four of 25 adult coeliacs, but not in 29 children with coeliac disease. Robinson *et al*[18] found spleens of small volume in 14 of 29 treated adult coeliacs, mean age 44 years, and found that the proportion of patients with small spleens increased with increasing age at diagnosis of coeliac disease. Splenic atrophy was demonstrated in 12 of 41 cases in this study and this is similar to studies of adults with coeliac disease but without malignancy. We have found, as did Robinson *et al,* that hyposplenic coeliacs tend to be older than coeliacs with normal splenic function.

It is possible that minor changes related to hyposplenism which may be overlooked in blood films could be detected using more sensitive techniques. The nature of this study made red cell clearance measurements or reproducible spleen scanning impossible, so that the figure of 12 hyposplenic patients may be an underestimate, but is unlikely to be an overestimate.

Coeliac disease and hyposplenism are not particularly associated with malignancy in this series and there was no relationship between hyposplenism and the type of malignancy. This suggests that the patient with coeliac disease and hyposplenism is no more at risk of developing malignancy in general or lymphoma in particular than if his splenic function were normal.

We are greatly indebted to the numerous clinicians throughout the country who have reported patients for inclusion in the National Study of Coeliac Disease and Malignancy, set up after a meeting at the Clinical Research Centre, Harrow, in November 1978, and, in particular, to those who have sent blood samples from patients under their care.

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