Lymphoma in coeliac disease

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J R Soc Med 1995;**88**:672–677

Keywords: *coeliac disease; malignant lymphoma; enteropathy associated T-cell lymphoma; gluten-sensitive enteropathy*

INTRODUCTION

As early as in 1937, Fairley and Mackie drew attention to a sprue-like syndrome occurring in patients with intestinal reticulosis[1]. They stressed the clinical and biochemical similarities between their cases and those of idiopathic steatorrhoea. Gough *et al.* were the first to suggest that intestinal reticulosis may arise as a complication of idiopathic steatorrhoea and that the widespread mucosal derangement in idiopathic steatorrhoea was itself a premalignant condition[2]. Debate followed as to whether malignancies elsewhere in the body may induce secondary changes in the small intestinal mucosa, including the flattened appearance as seen in idiopathic steatorrhoea. The increased incidence not only of reticulosis but also of carcinomas in patients with idiopathic steatorrhoea refuted the belief that villous atrophy was a non-specific and secondary reaction to cancer elsewhere. Reports from the UK (mainly from Bristol and Birmingham), Ireland, Australia and the Scandinavian countries have confirmed the increased incidence of malignant lymphoma and cancer of the oesophagus, larynx and small intestine in coeliac disease (Table 1)[3–15]. Compared to non-coeliacs, patients suffering from coeliac disease have a 1.9 to 2.1 increased risk of dying[6,14]. The relative risk of dying from all malignancies or from lymphoma is described in Table 2. A 25- to 120-fold increased risk of malignant lymphoma is apparently present. The true risk, however, can be defined only when all, or most, patients with coeliac disease are identified in a defined population and longitudinal observations are obtained[16]. The incidence of coeliac disease in a population is not accurately known, lymphomas may remain undiagnosed unless autopsies are performed routinely, and patients with established lymphoma may have coeliac disease, but are usually not investigated from that point of view[17], except in two studies[18,19].

CONFUSING TERMINOLOGY

Before the introduction of the intestinal biopsy, idiopathic steatorrhoea was used in adults as synonymous with childhood coeliac disease. Nowadays, coeliac disease and adult coeliac disease (ACD) are preferred over gluten-sensitive enteropathy, coeliac sprue and non-tropical sprue[12]. According to the European Society for Paediatric Gastroenterology[20] coeliac disease is present, when a syndrome of clinical and biochemical malabsorption is accompanied by a flat jejunal biopsy, characterized by villous atrophy, crypt hyperplasia, a lymphoplasmocellular infiltrate in the lamina propria and an increased number of intra-epithelial lymphocytes. Further requirements are the complete clinical, biochemical, and histological restoration to normal after gluten withdrawal and reappearance of abnormalities upon gluten challenge. The last requirement is often not fulfilled in adult coeliac disease[21]. These criteria also do not take into account the condition of transient gluten intolerance and exclude asymptomatic relatives of coeliac patients with abnormal jejunal biopsies[22]. The term gluten-sensitive enteropathy has the disadvantage of not including patients with genuine coeliac disease who do not respond to gluten withdrawal (unresponsive or unclassified sprue), but sometimes react favourably to corticosteroids or immunosuppressive drugs[23].

Even more confusion is present in lymphoma due to the many synonyms such as Hodgkin's disease, Hodgkin's sarcoma, reticulum cell sarcoma, lymphosarcoma, immunoblastic sarcoma, histiocytic and lymphocytic lymphoma, unclassified lymphoma and undifferentiated large-cell lymphoma[24]. These terms were used to describe the pleiomorph infiltrate of lobulated, indented, multinucleated medium-sized to large cells with complex nuclei, prominent nucleoli and abundant cytoplasm, often resembling Reed-Sternberg cells. In 1978 Isaacson and Wright considered that all mentioned cases were a variant of malignant histiocytosis of the intestine, a diffuse intestinal wall infiltration without solid tumour masses, usually accompanied by eosinophils and plasma cells, spreading to liver, spleen, lymph nodes, bone marrow and skin[25]. In addition, both authors believed that this tumour caused most, if not all, cases of ulcerative jejunitis[26,27]. They demonstrated the true histiocytic, i.e. monocyte/macrophage, derivation of the tumour with (erythro)phagocytosis, positive staining for non-specific fluoride sensitive esterase, acid phosphatase and α1-antitrypsin. The positive staining for α1-antitrypsin was considered to be a highly reliable and specific marker for benign and malignant histiocytes and shown to be synthesized

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Table 1 **General mortality rate and mortality rate of malignancies and lymphoma (and when indicated morbidity rates) in adult coeliac disease**

Author	Country	Coeliac population at risk	All deaths	All deaths (%) due to malignancy	All deaths due to lymphoma
Harris (Ref 4)	Birmingham, UK	202	77	31 (15.3)	14
Whorwell (Ref 5)	Coeliac Society, UK	(5000)	77	31	10
Holmes (Ref 6)	Birmingham, UK	202	97	37 (18.3)	18
		210	43	21* (10.0)	13*
Selby (Ref 8)	Australia	93		11* (11.8)	4*
Cooper (Ref 9)	Birmingham, UK	385	118	55 (14.3)	27
O'Driscoll (Ref 10)	Ireland	198		16* (8.1)	10*
Swinson (Ref 11)	UK Survey	235		259*†	133*†
Haagen Nielsen (Ref 12)	Denmark	100	23	9* (9.0)	3*
Holmes (Ref 13)	Birmingham, UK	210	69	31* (14.8)	9*
Logan (Ref 14)	Lothian, UK	653	115	44 (6.7)	17
McCarthy (Ref 15)	Ireland		53	28	13

*Cancer morbidity data
†More cancers per patient

Table 2 **Relative risk of dying from malignancy or lymphoma in adult coeliac disease**

			All deaths due to malignancy			All deaths due to lymphoma		
Author	Country	Sex	O	E	O/E	O	E	O/E
Harris (Ref 4)	Birmingham, UK	♂	22	4.97	4.42*	9	0.067	134*
		♀	9	4.38	2.05*	5	0.048	104*
		All	31	9.35	3.32*	14	0.115	122*
Whorwell (Ref 5)	Coeliac Society, UK	♂	15	10.8	1.39	5	0.2	25*
		♀	16	11.5	1.39	5	0.2	25*
		All	31	22.3	1.39	10	0.4	25*
Holmes (Ref 6)	Birmingham, UK	♂	12	2.88	4.17*	6	0.062	97*
		♀	9	2.17	4.15*	7	0.052	135*
		All	21	5.05	4.16*	13	0.114	114*
Selby (Ref 8)	Australia	♂	3	0.58	5.19*	1	0.028	36*
		♀	7	1.23	5.67*	3	0.051	59*
		All	10	1.81	5.52*	4	0.079	51*
Haagen Nielsen (Ref 12)	Denmark	♂	2	0.83	2.41?			
		♀	7	1.03	6.80?			
		All	9	1.86	4.83?			
Holmes (Ref 13)	Birmingham, UK	♂	19	7.38	2.57*	7	0.10	70*
		♀	12	8.10	1.48	2	0.11	18**
		All	31	15.48	2.00*	9	0.21	43*
Logan (Ref 14)	Lothian, UK	♂	24	6.9	2.97*	8	0.24	33*
		♀	20	7.9	3.48*	9	0.30	30*
		All	44	14.8	2.97*	17	0.54	31*

O=Observed; E=expected; O/E=ratio observed/expected=relative risk
*$P<0.001$ **$P<0.01$; ?=statistics not given
†Proportional statistics

by monocyte and macrophage cells[26,27]. It is amazing that they then already alluded to difficulties in separating malignant histiocytosis of the intestine from T-cell lymphoma[26]!

O'Farrelly *et al.* called the intestinal lymphoma associated with abnormal jejunal histology, the enteropathy-associated T-cell lymphoma (EATCL)[28]. They coined the term EATCL as they questioned whether villous atrophy seen in association with the lymphoma represented true coeliac disease, as patients with this type of lymphoma lacked antibodies to α1-gliadin. Others suggested EATCL to be a tumour arising from a mucosa-committed T-cell, probably an intra-epithelial lymphocyte[29,30]. Gradually, cytochemical and immunohistochemical stainings and cytogenetic studies elucidated the T-cell origin of the lymphoma[29–31]. The specific marker profile of the lymphoma can be explained by partial antigenic deletion of the phenotype which characterizes the majority of normal intra-epithelial lymphocytes[32]. T-helper/inducer-associated antigen (CD4) and T-suppressor/cytotoxic-associated antigen (CD8) as well as pan-T-antigens CD1, CD2 and CD3 (antigen associated with the T-cell receptor) were often undetectable. The CD7 antigen was mostly present[27,29,33]. Positive enzymatic staining is no longer considered a specific marker for histiocytes, but appeared also to be present in T-cell lymphomas[27].

Many investigators agreed about the pattern of T-cell lymphoma (EATCL) being HML–1+CD7+CD3±CD4–CD8–, with CD3 becoming negative as the tumour progressed[19,29,33]. Gene rearrangement studies and DNA hybridization techniques recently showed a rearranged T cell receptor beta chain, which may assist in earlier diagnosis of the lymphoma: the neoplastic T-cell clone may be detected in coeliac disease before a tumour mass is evident[27,34]. The relationship of the recently discovered increased gamma/delta T-cell receptors to lymphoma is as yet unclear[33,35].

T-cell lymphoma as a complication of adult coeliac disease has to be distinguished from PSIL (primary small intestinal lymphoma), which arises focally from lymphoid tissue with the remaining small bowel being uninvolved and from IPSID (immunoproliferative small intestinal disease), a B-cell lymphoma involving the complete small bowel[36]. For grading into high and low grade malignancy the updated Kiel classification is used[37]: the Ann Arbor system, devised for Hodgkin lymphoma, with Musshoff's modification is used for staging[38,39].

CLINICAL DIAGNOSIS

Relapse or failure to respond to a gluten-free diet in a patient previously shown to have a complete remission, non-responsiveness from the outset in a newly diagnosed coeliac patient or the occurrence of persistent pyrexia, abdominal pain and profound muscle weakness are all ominous signs. Also weight loss, diarrhoea and skin rashes are often present. Opportunistic infections may also present acutely[2,3,9].

Diagnosis is sometimes made at autopsy (in 21–30%)[4,9]. Often, emergency laparotomy is needed because of perforation, bleeding or obstruction[3,9,18], the more so in ulcerative jejuno-ileitis[40], which on the one hand may be fortunate as early resection is associated with a better survival, but on the other hand will not be survived by the rapidly deteriorating patient[3,11,41]. Diagnostic laparotomy is often required. Full-thickness wall biopsies, liver biopsy, spleen biopsy, and lymph node tissue should be taken and enough fresh and frozen tissue should be obtained for extensive cytogenetic and (immuno)histochemical examination. By re-examining the histology with the current more refined typing facilities we could establish (in retrospect) a more appropriate diagnosis in four, an 0.6-year earlier diagnosis in six and an upgrade stage of disease in two out of 14 patients with EATCL and coeliac disease[19].

The diagnosis is highly problematic when both diseases make their clinical presentation within a short time of each other. In patients who had malabsorption and a flat jejunal mucosa, with clinical, biochemical and histological restoration to normal upon a gluten-free diet and who develop subsequently a lymphoma, this lymphoma then is considered to complicate coeliac disease. In general, 8 years lapsed between the diagnosis of coeliac disease and lymphoma, whereas the length of symptoms of lymphoma from onset to diagnosis averaged 9 months[9].

When the lymphoma is detected together with a typical coeliac mucosa remote from the tumour, a positive response to gluten-free diet is rather unusual[9]. In the early stage lymphoma there will be no symptoms or symptoms are misinterpreted as benign chronic ulcerative non-granulomatous jejuno-ileitis—a condition also reported to complicate coeliac disease[18,25,42]. In mild or asymptomatic adult coeliac disease the diagnosis will often be made fortuitously via a jejunal biopsy[4]. The size of the problem is well demonstrated in Swinson's study, in which 156 (66.4%) patients had the sequence adult coeliac disease followed a mean of 7.3 years later by a lymphoma[11]. However, 44 out of 235 (18.7%) had both diseases simultaneously, and in another 14.9% (35/235) the diagnosis of coeliac disease followed the diagnosis of malignancy. In Cooper's study[9] coeliac disease and lymphoma appeared concurrently in 37% (10/27), in Holmes' study[6] in 29% (6/21), in our study[19] in 21% (3/14).

There are several arguments in support of malignant lymphoma as a complication of coeliac disease[33]. First-degree relatives are at risk of getting coeliac disease and/or malignancy[43,44]; HLA typing is similar in coeliac disease and lymphoma without a specific typing associated with the development of malignancy in adult coeliac disease[10,11,45]; splenic atrophy is present in both diseases[46,47]; both diseases

have the same intra-epithelial lymphocyte populations[33] and, in the case of malignant lymphoma, the coeliac mucosa will return to normal, but only after resection or chemotherapeutic treatment of the lymphoma[18,19,48,49].

Some investigators persist in claiming an independent and primary role for the malignant lymphoma[28,32,50,51]. They all presume a preceding low grade intra-epithelial lymphocyte lymphoma, which leads via villous atrophy, crypt hyperplasia and intra-epithelial lymphocytosis to malabsorption, which is of course not sensitive to gluten. The common presentation of the EATCL with worsening of malabsorption, with bleeding, perforation, or obstruction is usually associated with evolution to a high-grade lymphoma. The response to gluten-free diet, seen in some patients with EATCL, is ascribed to the removal of antigenic dietary proteins from an already chronically damaged intestine.

PROGNOSTIC PARAMETERS

Despite some long-term survivors after surgical resection, radiotherapy, and chemotherapy, survival is poor[11,15,18,19]. In Cooper's study[9] the time of onset of lymphoma to death was a mean of 9 months in 25 out of 27 patients, in Swinson's survey[11] the 5-year survival rate was 9.5%. Early diagnosis and discovery of prognostic factors are mandatory. Several prognostic factors can be mentioned, such as age, sex, compliance and response to a gluten-free diet, histological parameters, blood parameters, stage of the disease and delay in diagnosis. Even in 1967, Harris *et al.*[4] stated that a high degree of suspicion should be present with men over 40 years of age with a history of coeliac disease for more than 10 years and not on a gluten-free diet. At a later date, Cooper *et al.*[52] investigated the age specific lymphoma rate in 314 patients with coeliac disease, 20 patients were found to have developed a lymphoma. The incidence of lymphoma between 51 and 80 years was 3 to 11 times higher than in the 4th and 5th decade. In 12 patients the lymphoma was diagnosed within 4 years of the diagnosis of coeliac disease. This means, that lymphoma is particularly a complication of elderly coeliacs and that patients newly diagnosed as having coeliac disease at more than 50 years of age should be closely followed, for they have a 1 in 10 chance of harbouring a lymphoma which will become manifest within the next 4 years.

Several histological and biochemical data are of prognostic and diagnostic value. Aggregation of histiocytic cells, histiocyte aggregates at the base of ulcers in chronic ulcerative non-granulomatous jejuno-ileitis, a low plasma cell count in the lamina propria, lower lymphocyte numbers in the epithelium and higher numbers in the lamina propria are ominous signs[17,24,42]. Ferguson *et al.* showed that the last three features tended to be present for up to 5 years before the diagnosis of lymphoma was made[53]. Rising IgA levels after prior normalization on a gluten-free diet may be a warning sign[9]. The lymphocyte response to mitogens and antigens has been reported as subnormal or normal in patients with coeliac disease complicated by lymphoma[54,55]. One study suggested an increase in percentage of peripheral B lymphocytes was a marker of concurrent lymphoma in coeliac disease[55]. Serum lysozyme activity could not be recommended as a diagnostic marker[56], but recently two interesting aids to the diagnosis of lymphoma in patients with coeliac disease have been put forward[57–59]. Diamine oxidase in plasma, both basal and after heparin injection, reflects the morphological and functional condition of enterocytes. Plasma levels are the highest in normals and successfully treated coeliac disease and lower in ranking order of untreated or unresponsive coeliac disease and lymphoma[57]. Placental lactoferrin or placental ferritine is present in 40–50% of CD4+ lymphocytes in the lamina propria and in differentiated malignant cells of EATCL: it is absent in peripheral T-cells or intra-epithelial lymphocytes. Blood levels are high in active, untreated coeliac disease and should lower and normalize in well-treated gluten-sensitive enteropathy. Persistent high levels are prognostic of a higher risk of lymphoma[58,59].

Lymphoreticular dysfunction and hyposplenism were extensively investigated, because of the interest in the part immunological insufficiency may play in the development of malignant lymphoma[46,47]. Hyposplenism was not seen in children with coeliac disease and increased with age and with duration of exposure to dietary gluten. It was, however, not associated with the development of malignancy and fluctuated with the activity of the disease, being largely functional and reversible, but finally irreversible in the case of atrophy of the spleen.

ROLE OF GLUTEN-FREE DIET

A gluten-free diet often results in symptomatic, clinical, haematological, biochemical and histological improvement in coeliac disease. In late follow-up, however, the compliance to the diet is poor. In two paediatric follow-up studies, the principal reason for lack of compliance was not lack of knowledge of the disease or lack of understanding the diet, but the surprising lack of symptoms and apparent morbidity[60,61]. In 102 adolescents, some defect in growth was present in all, anaemia was present in 24, but only two patients sought medical advice because of complaints of iron deficiency anaemia. A reticulosarcoma of the ileum was the cause of death in one patient (0.8%)[61]. In 123 teenagers with a follow-up of 10 years after diagnosis of coeliac disease in the first 3 years of their lifes, 65% were compliant with the diet, 11.4% were occasionally not compliant and 23.6% were non-compliant. Small amounts of gluten per day (0.06–2.0 g) produced a decrease in surface epithelial

volume, an increased crypt epithelial volume and increased intra-epithelial lymphocytes in the crypts[62].

The Birmingham group followed their patients over three time periods: from 1941 to 1965[4], from 1965 to 1975[6] and from 1975 to 1985[13]. In the first two periods, 202 patients with biopsy proven adult coeliac disease or idiopathic steatorrhoea (no biopsy) were included. From 1965 on, a second group of only biopsy proven adult coeliac disease patients (n=210) was considered. In the first study, a significant reduction of malignant complications was seen in those on a gluten-free diet for more than 12 months, especially in women[4]. In a later study, in biopsy proven coeliac disease, an excess of death from all malignancies and lymphomas was seen compared to the general population, irrespective of whether a conventional diet or a gluten-free diet was taken[6]. That study also showed no evidence to suggest, that those with a poor response to a gluten-free diet were more liable to develop malignant complications. In the last study, an excess morbidity was seen for all cancers of: (a) 11 times on a normal diet; (b) 5 times on a reduced gluten diet; and (c) 1.2 times on a strict gluten-free diet, with a morbidity comparable to normal non-coeliacs[13]. The relative risk of getting a lymphoma was 77.5 on a conventional diet compared to 16.7 on a gluten-free diet. No lymphoma was detected in those adhering to the gluten-free diet for more than 10 years, compared to an 80-fold relative risk on prolonged conventional diets. In those compliant less than 10 years the relative risk was 44 compared to a relative risk of 100 on a normal diet.

The question arises, whether gluten responsiveness in itself might be predictive. Barry and Cook looked at differences between patients responding to a gluten-free diet and those who did not respond[63]. The non-responders showed a decreased epithelial shedding, a decreased total mucosal thickness and lower mitotic index, suggestive of a lower cell turnover and a hypoplastic mucosa. They suggested that subtotal villous atrophy with a decreased cell turnover carried a particularly poor prognosis as half of these patients died from lymphoma. Interestingly, Marsh in a recent study distinguished several mucosal types in coeliac disease and mentioned also the hypoplastic mucosa[64]. He, however, considered the lamina propria—and not the intra-epithelial lymphocyte[22]—as the major site for the gluten-driven immunological and secondary inflammatory processes, emphasizing the role of MHC-2 class activated macrophages and CD4+ lymphocytes. In the blood, α1-gliadin antibodies were used as markers for two forms of enteropathy: one that is benign and sensitive to wheat protein, whereas the other runs a malignant course[28]. These antibodies are raised in uncomplicated and untreated coelic disease and normalize in those patients, who respond favourably to gluten withdrawal. The absence of α1-gliadin antibodies with otherwise normal humoral responses, especially in male coeliacs unresponsive to a gluten-free diet, appeared to be associated with EATCL[28].

CONCLUSION

Although it is generally accepted that coeliac disease may be complicated by malignant lymphoma and that a proper and timely diagnosis requires clinical vigilance, the coincidence of both these rare diseases remains an enigma. The reason why patients who have coeliac disease diagnosed in childhood rarely develop lymphoma whilst those who are diagnosed later in life more commonly develop this complication remains unclear. Further research is needed to establish why these groups have apparently different clinical courses, as this may provide a clue to pathogenesis of this disease.

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(Accepted 19 April 1995)