Low carbohydrate diets are currently being promoted as an effective treatment for weight reduction. The most popular, the Atkins’ diet, is a worldwide bestseller with over 10 million book copies sold (the earliest printing was in 1997). Novel presentation of coeliac disease after following the Atkins’ low carbohydrate diet

The diet remains low in cereal grains (wheat, barley, rye, and potatoes, and rice but including fruit and vegetables). In the longer term maintenance phase, mainly as unlimited protein and fat intake, with carbohydrate diet (cutting out bread, pasta, and other starchly vegetables). In the longer term maintenance phase, the diet remains low in cereal grains (wheat, barley, rye, and potatoes, and rice but including fruit and vegetables).

We report three patients seen in the last year who sought medical advice because of symptoms noticed after stopping the Atkins’ diet, which subsequently proved to be due to coeliac disease.

Case No 1
A 46 year old woman, with coexisting treated primary hypoadrenalism and autoimmune hypothyroidism, followed the Atkins’ dietary regimen strictly as published. She described “feeling amazing” and “wide awake” on the regimen. After six months she lost 12 kg and decided to reintroduce bread. She soon noticed bloating, tiredness, and upper abdominal pain. Her physician suspected coeliac disease and initiated testing for antidiomysial antibody (positive), with subsequent diagnostic duodenal biopsy (crypt hyperplastic partial villous atrophy). All symptoms resolved on a gluten free diet.

Case No 2
A 45 year old woman, with coexisting treated autoimmune hypothyroidism, followed the Atkins’ diet strictly as published for three months, losing 7 kg. On this regimen she described feeling “really well” and “fantastic”. On reintroducing bread she noticed symptoms of tiredness, abdominal gurgling noises, and pain, and increased flatulence. Her father was diagnosed with coeliac disease around this time. These symptoms led her to suspect coeliac disease. Subsequent tests showed positive antidiomysial antibody and small intestinal crypt hyperplastic partial villous atrophy. Her symptoms resolved on a gluten free diet.

Case No 3
A 45 year old woman who commenced a low carbohydrate diet (cutting out bread, pasta, potatoes, and rice but including fruit and vegetables) noticed increased wellbeing on this regimen. She reintroduced some bread at one month and noticed abdominal bloating and pain, with increased tiredness. These symptoms led her to suspect coeliac disease. Her physician found iron deficiency anaemia and subsequent tests showed positive antidiomysial antibody and small intestinal crypt hyperplastic partial villous atrophy. Her symptoms resolved on a gluten free diet except for occasional abdominal bloating.

Recent large studies (rallying highly sensitive and specific serological screening tests) have suggested coeliac disease is much more prevalent (~1%) in the UK population than previously recognised. In addition to those symptoms presenting clinically, untreated coeliac disease has silent features, including anaemia, osteoporosis, and modest increases in overall risks of malignancy and mortality. In a recent prospective study of seven year old children, those with positive coeliac serology were significantly shorter and lighter. Awareness of coeliac disease has recently been increasing, and all major UK supermarket chains now stock a varied range of gluten free products.

Symptoms induced by wheat ingestion in coeliacs are often more marked after a period following a gluten free diet than occur prior to diagnosis and treatment. Consistent with this observation, interal y peripheral blood β-cell responses to the immunodominant A-gliadin epitope (QLQFPQQPELPYPQPQS) after short term oral gluten challenge are not observed in untreated coeliac cases but are detectable in significant numbers after two weeks of a gluten free diet. The immunological basis of the heightened sensitivity after gluten withdrawal is unknown but intestinal immune responses to antigen are likely to be downregulated in conditions of ongoing chronic inflammation compared with those occurring in normal (treated) mucosa. Although some individuals will have simple wheat intolerance, we conclude that the occurrence of gastrointestinal symptoms after a period following an Atkins-type low carbohydrate diet should prompt investigation for coeliac disease.

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References


Cap polyposis: an inflammatory disorder or a spectrum of mucosal prolapse syndrome?

We read with great interest the letter by Maunoury and colleagues (Gut 2005;54:313–14). They reported on a case of cap polyposis unresponsive to infliximab, in contrast with the successful report by Bookman and colleagues. Maunoury et al stated that the success with infliximab reported by Bookman et al might have been due to spontaneous regression of cap polyposis. Maunoury et al speculated that a role for tumour necrosis factor α (TNF-α) in the pathogenesis of this rare disorder was unacceptable and other mechanisms, such as abnormal colonic motility, may be important.

The pathogenesis of cap polyposis has been controversial. In particular, there have been discussions about whether cap polyposis is a specific form of inflammatory disorder or part of a spectrum of “mucosal prolapse syndrome” which is caused by abnormal colonic motility with subsequent local ischaemia and repeated mucosal trauma. We recently experienced a case of cap polyposis, highly suggestive of a role of inflammation in the progression of this disease.
Although the polyps were located in a line on the anastomosis, the adjacent mucosa was normal. She showed no clinical symptoms at that point and so no additional treatment was performed.

Two cases of recurrent cap polyposis after colorectal resection have been reported previously,\(^3\) of which one was very similar to the present case in that the recurrent polyps were located only along the anastomotic line.\(^1\) The process of wound healing on the anastomosis is known to involve a complex network of numerous inflammatory cells and their secretory products, including TNF-\(\alpha\), which accelerates the wound healing process by inducing angiogenesis, fibroblast proliferation, and production of several growth factors.\(^3\) Therefore, progression of cap polyposis confined along the anastomotic line observed both in the present case and in the report mentioned previously may provide evidence that local inflammation plays, at least in part, a role in the progression of cap polyposis. With acceptance on this point, suppression of inflammation could be a clue to treat cap polyposis, as in the case of metronidazole whose anti-inflammatory action plays a central role in the healing of cap polyposis.\(^6\)

**References**


**Figure 1** Endoscopic view of progression of cap polyposis confined along the anastomotic line three months after surgery. Note remission on the adjacent mucosa.

**Figure 1** Full thickness biopsy of the small intestine with haematoxylin-eosin. The section shows a normal mucosal layer of jejunum without atrophy or excessive amounts of round cells. The muscularis mucosae is also normal. In contrast, the muscularis propria shows a heavy lymphocytic infiltrate (haematoxylin-eosin). Insert: immunohistochemical stain for CD8 lymphocytes in the muscularis propria.
Our case showed a particularly affected muscle with a respected mucosa. In Rigby’s case, the muscular layer seemed to show fibrosis rather than inflammation. Our case showed a homogenous lymphocytic T infiltrate which is different from the polymorphic fibrosis rather than inflammation. Our case showed a homogenous lymphocytic T infiltrate which is different from the polymorphic fibrosis rather than inflammation. Our case showed a homogenous lymphocytic T infiltrate which is different from the polymorphic fibrosis rather than inflammation. Our case showed a homogenous lymphocytic T infiltrate which is different from the polymorphic fibrosis rather than inflammation. Our case showed a homogenous lymphocytic T infiltrate which is different from the polymorphic fibrosis rather than inflammation. Our case showed a homogenous lymphocytic T infiltrate which is different from the polymorphic fibrosis rather than inflammation. Our case showed a homogenous lymphocytic T infiltrate which is different from the polymorphic fibrosis rather than inflammation. Our case showed a homogenous lymphocytic T infiltrate which is different from the polymorphic fibrosis rather than inflammation. Our case showed a homogenous lymphocytic T infiltrate which is different from the polymorphic fibrosis rather than inflammation. Our case showed a homogenous lymphocytic T infiltrate which is different from the polymorphic fibrosis rather than inflammation. Our case showed a homogenous lymphocytic T infiltrate which is different from the polymorphic fibrosis rather than inflammation. Our case showed a homogenous lymphocytic T infiltrate which is different from the polymorphic fibrosis rather than inflammation. Our case showed a homogenous lymphocytic T infiltrate which is different from the polymorphic fibrosis rather than inflammation. Our case showed a homogenous lymphocytic T infiltrate which is different from the polymorphic fibrosis rather than inflammation. Our case showed a homogenous lymphocytic T infiltrate which is different from the polymorphic fibrosis rather than inflammation. Our case showed a homogenous lymphocytic T infiltrate which is different from the polymorphic fibrosis rather than inflammation. Our case showed a homogenous lymphocytic T infiltrate which is different from the polymorphic fibrosis rather than inflammation. Our case showed a homogenous lymphocytic T infiltrate which is different from the polymorphic fibrosis rather than inflammation. Our case showed a homogenous lymphocytic T infiltrate which is different from the polymorphic fibrosis rather than inflammation. Our case showed a homogenous lymphocytic T infiltrate which is different from the polymorphic fibrosis rather than inflammation. Our case showed a homogenous lymphocytic T infiltrate which is different from the polymorphic fibrosis rather than inflammation. Our case showed a homogenous lymphocytic T infiltrate which is different from the polymorphic fibrosis rather than inflammation. Our case showed a homogenous lymphocytic T infiltrate which is different from the polymorphic fibrosis rather than inflammation. Our case showed a homogenous lymphocytic T infiltrate which is different from the polymorphic fibrosis rather than inflammation. Our case showed a homogenous lymphocytic T infiltrate which is different from the polymorphic fibrosis rather than inflammation. Our case showed a homogenous lymphocytic T infiltrate which is different from the polymorphic fibrosis rather than inflammation. Our case showed a homogenous lymphocytic T infiltrate which is different from the polymorphic fibrosis rather than inflammation. Our case showed a homogenous lymphocytic T infiltrate which is different from the polymorphic fibrosis rather than inflammation. Our case showed a homogenous lymphocytic T infiltrate which is different from the polymorphic fibrosis rather than inflammation. Our case showed a homogenous lymphocytic T infiltrate which is different from the polymorphic fibrosis rather than inflammation. Our case showed a homogenous lymphocytic T infiltrate which is different from the polymorphic fibrosis rather than inflammation. Our case showed a homogenous lymphocytic T infiltrate which is different from the polymorphic fibrosis rather than inflammation. Our case showed a homogenous lymphocytic T infiltrate which is different from the polymorphic fibrosis rather than inflammation. Our case showed a homogenous lymphocytic T infiltrate which is different from the polymorphic fibrosis rather than inflammation. 

Table 1: Clinical and histological features of our present case and cases in the literature

<table>
<thead>
<tr>
<th>Sex/age (y)</th>
<th>Histological features</th>
<th>Treatment</th>
<th>Evolution</th>
<th>True lymphocytic intestinal leiomyositis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present case</td>
<td>F 16</td>
<td>T lymphocytic infiltrate in muscularis propria</td>
<td>Steroids and later budesonide. Azathioprine</td>
<td>Mild symptoms, oral nutrition 2 y later</td>
</tr>
<tr>
<td>Nezelof⁴</td>
<td>M 6 mo</td>
<td>Mononuclear infiltrate in muscularis propria</td>
<td>Steroids</td>
<td>Mild symptoms, oral nutrition 2 y later</td>
</tr>
<tr>
<td>Russka⁴</td>
<td>M 2</td>
<td>Predominant T lymphocytic infiltrate</td>
<td>Steroids, azathioprine, tetracycline, and eosinophils</td>
<td>Total PN</td>
</tr>
<tr>
<td>Mann⁴</td>
<td>M 47</td>
<td>Chronic inflammatory infiltrate + fibrosis of longitudinal muscle</td>
<td>NR</td>
<td>Death 2 y later</td>
</tr>
<tr>
<td>Rigby³</td>
<td>F 27</td>
<td>Predominant fibrosis of the circular layer</td>
<td>Immunosuppression</td>
<td>Oral diet plus gastrostomy feeds. Alive at 21 months</td>
</tr>
<tr>
<td>Ginie`s³</td>
<td>F 6 mo</td>
<td>Very polymorphic infiltrate: lymphocytes, plasmocytes, histiocytes, and eosinophils</td>
<td>Steroids</td>
<td>Oral nutrition. Normal weight and height</td>
</tr>
<tr>
<td>McDonald⁴</td>
<td>cases 1/2/3/4</td>
<td>Mucosa predominantly affected</td>
<td>Cyclophosphamide and steroids/stereoids</td>
<td>Mild symptoms at 9 y/PN one year later/NR/NR</td>
</tr>
<tr>
<td>Arista-Nasr⁴</td>
<td>cases 1/2/3</td>
<td>Mucosa predominantly affected</td>
<td>Cyclophosphamide/ tetracycline, tindazol, PE/tetracycline, steroids, chemotherapy</td>
<td>Death from inanition/ death from inanition/alive, severe inanition</td>
</tr>
</tbody>
</table>

M, male; F, female; NR, not reported; PN, parenteral nutrition; PE, pancreatic enzymes.

UK guidelines for management of acute pancreatitis: is it time to change?

The incidence of acute pancreatitis is increasing in the UK, with a current hospital admission rate of 20 per 100 000 population. However, there has been only a marginal decrease in the overall one year case fatality rate, from 12.7% in 1975–86 to 11.8% in 1987–98. Gall stones and alcohol are the main aetiological factors for acute pancreatitis. Nearly 25% of episodes of acute pancreatitis are severe and approximately 45% of these are due to gall stones. The UK guidelines for the management of acute pancreatitis were formulated and released by the British Society of Gastroenterology (BSG) in 1998. MEDLINE, EMBASE, and the Cochrane databases were searched to find recent evidence in the management of acute pancreatitis. The search terms included pancreatitis (MeSH), sphincterotomy-endoscopic (MeSH), cholangiopancreato-gram magnetic resonance (MeSH), acute NEAR (text), MRCP (text), ERCP AND sphincterotomy (text). A management plan, modified from the BSG guidelines in light of the new evidence available since its release in 1998, is proposed in fig 1. Firstly, acute pancreatitis is stratified according to severity. Glasgow-Imrie scoring together with C reactive protein are recommended by the BSG for stratification of severity of acute pancreatitis. However, with the availability of one stop tests, such as urinary trypsinogen activation peptide, and with the likelihood of mild acute pancreatitis transforming into severe acute pancreatitis being rare, severity stratification of pancreatitis can now be performed on admission. 

The next step is to determine aetiology. Imaging to find aetiology should be performed within 24 hours, in contrast with the BSG recommendations of a CT scan between three and 10 days. The rationale behind imaging within 24 hours is to facilitate early endoscopic retrograde cholangiopancreatography (ERCP) and sphincterotomy, as there is strong evidence that ERCP and sphincterotomy performed less than 72 hours decreases the complication rate in acute severe gall stone pancreatitis. This imaging, within 24 hours during the acute resuscitation phase, is made possible because of the shorter time to perform spiral computed tomography (CT) of the abdomen, which has a high sensitivity and specificity in diagnosing cholelithiasis. If the aetiology is still unknown after the CT scan, a magnetic resonance cholangiopancreatogram (MRCP) may be performed, as this has a higher sensitivity than the CT scan in the diagnosis of choledolithiasis. A simple calculation based on the incidence of pancreatitis (9.8 per year per 100,000 population), the incidence of severe pancreatitis (approximately 25%), and the incidence of gall stones as the aetiological factor in acute severe pancreatitis (45%) reveals that severe acute gall stone pancreatitis has an incidence of approximately 1.1
Aetiology so that ERCP and sphincterotomy MRCP in the diagnosis of choledocholithiasis pancreatitis. Also, because of the accuracy of cholangiopancreatography; ERCP, endoscopic retrograde cholangiopancreatography; CT, computed tomography; HDU, high dependency unit; ITU, intensive therapy unit.

In conclusion, a review of the UK guidelines for the management of acute pancreatitis. MRCP, magnetic resonance cholangiopancreatography; ERCP, endoscopic retrograde cholangiopancreatography; CT, computed tomography; HDU, high dependency unit; ITU, intensive therapy unit.

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RANK ligand and osteoprotegerin: emerging roles in mucosal inflammation

We read with interest the study by Byrne and colleagues (Gut 2005;54:79–86) outlining the significant therapeutic opportunities provided by manipulation of the RANK/RANK ligand (RANKL)/osteoprotegerin (OPG) system using recombinant Fc-OPG. There are, however, a number of physiological effects of OPG that were not discussed and which demonstrate the depth of influence of the RANK/RANKL/OPG system on both inflammatory disease and possibly immune surveillance mechanisms. These additional actions may provide both novel therapeutic approaches in inflammatory disease and point to other clinical effects of the Fc-OPG construct.

Work published by our own group1 studying the interleukin 2 deficient mouse model of inflammatory bowel and bone disease, using identical doses of Fc-OPG to Byrne et al, demonstrated the effects on gut inflammation, dendritic cell (DC) numbers, and macrophage (Mo) activation, as analysed by both colonic histology and flow cytometry. In the April issue of Gut, Moschen and colleagues (Gut 2005;54:479–487) showed that OPG can be demonstrated on both DC and Mo, also indicating that the molecule has the potential to influence these cells. These observations are in keeping with previous publications which have outlined the role of the RANK/RANKL/OPG system in DC survival, function, and the development of antigen specific memory T cell responses.2 Hence modulation of inflammatory responses in the gut using Fc-OPG could theoretically provide both direct treatment for gut inflammation alongside the associated bone loss described by Byrne et al. OPG has also been shown to influence TRAIL mediated signalling3 which may also impact on the DC microenvironment, preventing DC death, but more significantly has shown effects in prevention of TRAIL induced apoptosis in a number of tumour types.4,5

These findings highlight the fact that OPG can significantly influence survival of different cell types and the full extent of the actions of Fc-OPG in vivo are undoubtedly still yet to be shown.

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Synbiotic therapy for ulcerative colitis

We read with interest the article by Furrie and colleagues (Gut 2005; 54:242–9). While we believe this approach represents a very interesting advance in our understanding of aspects of the mucosal response to synbiotic therapy in ulcerative colitis (UC), we would like to raise some questions about the design of the study, which relate in particular to the conclusion that the synbiotic cocktail produces some improvement in disease activity in UC. Five patients were taking steroids, and six patients were taking immunosuppressants in each of the active treatment and placebo groups (see table 2). While the study design states that no treatment changes were made once the patients were started on test therapy, no information is given as to whether the steroids or immunosuppressants were started or had their dose changed, in the period immediately before the test therapy began. Given that the lag between recruitment and initiation of the test treatment was up to two months, we need reassurance that no treatment changes were made during this period that could have contributed to the later clinical and histological changes associated with the test therapies.

Two of the outcome measures seem to have been scores of sigmoidoscopic appearance and microscopic disease activity, which have not been previously validated formally. Can we be reassured that the conclusions drawn from these lag periods would have been the same had the authors used an unmodified Baron sigmoidoscopic score, and a more widely used histological activity index? Indeed, we note that there were in fact no significant changes after the synbiotic therapy in either the simple colitis activity index, sigmoidoscopic score (p = 0.06, using a t test which assumes normal distribution), bowel habit index, or histological score.

During the period between enrolment in the trial and initiation of the test treatment, one patient in the placebo group went into spontaneous remission (SCAI, modified Baron score 0) and so no longer fulfilled the entry criteria for the study. However, this subject still appears to have been included in the evaluation of the mucosal response to placebo and hence may have skewed the results for this group.

The authors reported a significant reduction in expression of mRNA for human beta- defensins 2–4 and the inflammatory cytokines tumour necrosis factor alpha and interleukin 1z in mucosal biopsies. It is of course possible that these changes might be associated with subsequent clinical, sigmoidoscopic, and endoscopic improvement, but we would question whether the data presented convincingly show initiation of the resolution of inflammation stated in the title. We agree with the authors that a much larger scale randomised controlled clinical trial of this synbiotic cocktail is needed, using conventional and well validated measures of response, before we can draw firm conclusions about its efficacy (or safety).

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Deranged smooth muscle α-actin expression as a biomarker of intestinal pseudo-obstruction

We read with interest the article by Knowles and colleagues (Gut 2004; 53:1583–9) in which the authors concluded that immunostaining of the adult jejunum with smooth muscle α-actin (ASMA) may be a valuable biomarker of chronic idiopathic intestinal pseudo-obstruction (CIIP). We recently published a similar study in which 17 archival formalin fixed, paraffin embedded samples of small intestine and 12 specimens of large intestine were immunostained with ASMA, desmin, and smooth muscle myosin heavy chain, using the same antibody for ASMA as Knowles and colleagues. In two of the three cases investigated in our study, ileal samples were examined from patients with clinical evidence of intestinal pseudo-obstruction. We found that both of these CIIP cases and all 15 control ileal samples showed weak or absent ASMA expression within the inner circular layer of the muscularis propria, with an identical pattern to that identified within the case and control ileal samples examined by Knowles et al.

Knowles et al found that 24% of CIIP cases showed absent or weak ASMA expression within the inner circular muscle ASMA expression within the jejenum while this pattern was not identified in any control jeunal samples. However, in the ileum, absent or weak ASMA expression was universal in their controls and present in 69% of CIIP cases.

It is possible that absent or weak inner circular muscle ASMA expression within the jejenum may represent a biomarker of CIIP.

However, the universal incidence of this phenomenon within the ileum in both studies and its presence at this site in a greater proportion of controls than cases, according to Knowles et al, indicates that ASMA expression should be interpreted with caution in these patients. In particular, although Knowles et al suggest that this phenomenon may be a biomarker of CIIP when identified within the jejunum, a definitive study of the geographical variation in ASMA expression within the muscularis propria of the small intestine is now indicated to determine the precise significance of this finding. The observation that manometric studies have shown pressure tracing patterns more suggestive of a neural defect than a primary muscular abnormality in most CIIP patients casts further doubt on the biological significance of apparent alterations in ASMA expression.

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Inflammatory biomarkers predict relapse in IBD

After reading the paper presented by Costa et al (Gut 2005; 54:364–8) and the additional commentary by Pardi and Sandborn (Gut 2005; 54:321–2), we would like to underscore the potential importance of biomarkers to assess intestinal inflammation and we would like to add a clarification on the faecal calprotectin assay.

We agree with Pardi and Sandborn that other serological markers have not demonstrated clinical utility as predictors or monitoring tools of inflammatory bowel disease (IBD) activity. Studies are emerging to support the sensitivity and clinical utility of more selective and specific non-invasive markers of intestinal inflammation, such as faecal calprotectin. As we deepen our understanding of the molecular basis of IBD, we may find that the degree of inflammation and its role in recurrence differs between Crohn’s disease and ulcerative colitis. This is an important question raised in both articles.

When comparing the Costa study with the earlier paper by Tibble and colleagues, one must ensure that the patient populations for each of the two disease states are equivalent. Disease activity was assessed at this site in a disease activity index (CDAI), a test that is highly subjective and correlates poorly with inflammatory activity assessed by In111 labelled white cells and endoscopic indices, both objective markers of disease activity. It is also clear from a recent analysis by Sands and colleagues that there is wide variation in how researchers apply the parameters of the...
CDAI. Saverymuttu* compared the excretion of In111 labelled leucocytes and found that the CDAI underestimated the degree of inflammation in 89% of patients with a CDAI <150 (that is, in clinical remission). This suggests that the CDAI does not necessarily reflect the inflammatory component of IBD.

Past studies (Tibble and Costa) demonstrated the clinical utility of faecal calprotectin in predicting remission in ulcerative colitis. Neither study makes clear the ability of biomarkers to predict remission in small bowel Crohn’s. CDAI as a marker of remission adds further confusion. The level of inflammatory biomarkers may vary anatomically based on neutrophilic flux, chronology, surface area, and disease process. Saverymuttu* found higher levels of In111 labelled leucocytes among large bowel Crohn’s compared with Crohn’s in the small bowel. Assessment of calprotectin as a predictor of relapse in small intestinal Crohn’s is an issue for future investigation, utilising objective evaluation of intestinal inflammation.

Finally, in addition to potential selection bias in the specificity and predictive value of calprotectin in small bowel Crohn’s disease, there is also an important misunderstanding regarding assay performance that should be clarified. The studies published by Tibble and colleagues* and most studies reported before 2003, evaluated faecal calprotectin using an earlier stool extraction process. The anti-calprotectin antibodies used in the earlier assay came from the same source. Eurospital has since developed an ELISA kit using the new extraction procedure and known calprotectin standards. The updated extraction process gives a five times higher yield during extraction of faecal calprotectin but does not change the performance of the kit in any other way. Thus the results in the Costa study in comparison with Tibble’s previous trial.

Colitis evolving into ulcerative colitis

We observed the development of ulcerative colitis (UC) in a 37 year old young woman with clinical and histological features of lymphocytic colitis (LC) after a period of 6 years. Seven years ago, the patient was admitted to our gastroenterology unit complaining of watery diarrhoea (>26 stools/day). She had never smoked and he was not taking any drugs affecting gastrointestinal secretion or motility. Laboratory tests, including autoimmune antibody and upper endoscopy, were normal. Parasitological and bacteriological faecal stools were negative. Biopsies of the jejunum did not show a pattern of coeliac disease. Colonoscopy with terminal ileoscopy was macroscopically normal. Ten biopsy specimens were taken from the rectum, revealing the histological pattern of LC (intraepithelial lymphocytes >10/100 epithelial cells) and erosion of the surface epithelium. In this way we obtained complete control of symptoms. Colonoscopy with biopsies of the rectum was repeated every year, confirming remission of the disease.

After six years the patient experienced abdominal pain and bloating with progressive worsening of diarrhoea. The stools became watery, sometimes bloody, and frequency was up to 8–10 times/day. She denied intake of non-steroidal anti-inflammatory drugs, ASA, or estro-progestin therapy. Parasitological and bacteriological faecal stools were negative. Colonoscopy was performed and revealed a macro granularity of the rectal mucosa with oedema and hyperaemia, and several erosions of the left colon were noted. No other lesions were found on the remaining colon or terminal ileum. Biopsies were taken and histology showed a moderately active ulcerative type. Laboratory tests were consistent with an elevated white blood cell count and increased inflammatory parameters. The patient was treated with oral prednisolone and 5-ASA (4.8 g/day). Complete remission of symptoms was obtained after two weeks of treatment. The patient continues to be in remission 18 weeks after the initial diagnosis of UC. She is still receiving 2.4 g/day 5-ASA, and oral prednisolone has been discontinued, with maintenance of resolution of symptoms.

In the literature, four cases of collagenous colitis (CC) evolving into UC have been reported* and two cases that developed into Crohn’s disease. This is the first case of LC evolving into UC. These phenomena suggest that both CC and LC could be part of a spectrum of inflammatory bowel diseases. The triggering factor in this transformation is still unknown. UC should be considered in patients with LC, if mucosal healing changes in their clinical course, with bloody diarrhoea and systematic features of UC.
Is there an ideal prognostic model for hepatocellular carcinoma?

We read with interest the paper by Greco et al. (Gut 2005; 54: 411–8). It is an elegant study that retrospectively compared the prognostic power among the Okuda, Cancer of the Liver Italian Program (CLIP), and Barcelona Clinic Liver Cancer (BCLC) staging systems for patients with hepatocellular carcinoma (HCC). The authors concluded that BCLC and CLIP were good models for non-surgical HCC, and BCLC had better predictive value compared with the others for patients with early stage HCC. As the CLIP system has been prospectively validated and proposed as the primary staging system for HCC, it would be interesting to examine how these commonly used HCC staging systems were derived and explore the potential limitations of the authors’ conclusions.

The main reason why the authors have reached this conclusion is probably related to the distinct characteristics of the study population. The majority (292 of 325, 89.6%) had undergone active treatment (percutaneous ablation or arterial chemoembolization), suggesting most had early or intermediate stage disease. These characteristics of the CLIP system, which contains treatment derived parameters,1 a prevailing model for prognostic prediction. A recent study comparing the various staging systems consistently showed that BCLC was best compared with CLIP, Okuda, and other systems in a surgically oriented referral centre.1 It should be noted that the CLIP and Okuda systems were originally derived from a large unselected patient population and the majority had been treated conservatively.2,3 Therefore, although the prognostic predictors selected for the currently used staging systems are not mutually exclusive, the derived predictive models from these predictors may have an otherwise variable differentiation power. Certain important risk factors, such as tumour size <3 or 5 cm, used in BCLC, can only be significant in the patient population that predominantly undergo auto locoregional therapies.2,3 In these instances, the predictive power of a given staging model, constructed from selected risk factors, could be drastically impaired if the majority of patients do not have early stage HCC. The majority may explain why the BCLC system is better than the CLIP and Okuda systems in the current study because clinical outcome was intimately associated with patient demographics and subsequent treatment strategy. Consistent with this notion is that a Canadian study group demonstrated that CLIP was a good predictive model for their HCC patients in whom more than half (52%) had only been treated conservatively due to a relatively advanced tumour or cirrhotic stage.2 Therefore, it is not surprising that BCLC is better that its competitors in an appropriate study environment.

In summary, the BCLC system contains treatment derived parameters and may work well in areas where HCC is diagnosed at a relatively early stage, whereas the CLIP or Okuda system would only prevail in patients with intermediate or late stage disease, under which conditions any aggressive forms of therapy are less likely to succeed. As the clinical presentation of HCC is tremendously heterogeneous, it is necessary to consider all known predictive factors, from early to advanced stages, in building an ideal staging system to fit all patient populations.

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Response to steroid therapy of sclerosing cholangitis after duodenopancreatectomy due to autoimmune pancreatitis

Autoimmune pancreatitis is a chronic inflammation of the pancreas due to aetiopathogenic mechanisms of autoimmunity. There are no established definitive diagnostic criteria although histological, analytical, and radiological characteristics enable us to identify this entity in the differential diagnosis with chronic autoimmune pancreatitis and pancreatic cancer.1 Nevertheless, this is not always possible, and the patient undergoes surgery with suspected cancer of the pancreas.2,3 Lymphoplasmacytic infiltration and autoantibodies (anti-IgG, anti-IgA, anti-GBM) may be only a minor finding, meaning the pancreas but can occasionally involve the retropancreatic and extrapancreatic biliary system. The relationship between the appearance of sclerosing cholangitis in patients with pancreatic pseudotumour due to autoimmune pancreatitis has even been considered the result of a systemic fibrolaminar response.4 We present the exceptional case of a patient who, after a cephalic duodeno-pancreatectomy due to pancreatic pseudo-tumour, in lymphoplasmacytic pancreatitis, presented with a clinical picture of post-surgical sclerosing cholangitis, which resolved after therapy with steroids.

In common with Komisawa and colleagues,5 we consider autoimmune pancreatitis a lesion more as part of a condition with multifocal fibrosis and we believe that this sclerosing cholangitis is an additional manifestation of an autoimmune systemic condition, possibly stimulated by surgery. A 78-year-old male patient was admitted to our service for obstructive jaundice of a few days’ history, not accompanied by constitutional syndrome. The patient had undergone surgery 75 days previously, with a preoperative radiological diagnosis of suspected cancer of the head of the pancreas. A radical pylorus preserving cephalic duodeno-pancreatectomy was performed. The patient was discharged 12 days after operation. The histopathology report of the resected sample revealed the presence of intense fibrosis and inflammatory, lymphoplasmacytic infiltration of the biliary wall with no evidence of malignancy. Similarly, the pancreatic gland presented with intense inflammation, lymphoplasmacytic, glandular atrophy, and no signs of malignancy. Biochemical work up on admission revealed: BBT 16.2 mg/dl; Bdd 12.2 mg/dl; GGT 1264 IU/l; ALP 831 IU/l; CEA 2.81 ng/ml; CA 19-9 >500 IU/ml; anti-IgG and anti-IgA HBsAg (–); HbcAg (–); HbcAc (–); anti-HCV (–); IgG 1520 mg/dl; IgA 445 mg/dl; IgG4 28 mg/dl; and IgM: 206 mg/dl. Abdominal echography showed dilation of the intrahepatic biliary tract. Magnetic cholangioresonance revealed moderate dilation of the complete intrahepatic tract with no visualisation of the principal biliary tract or hilar plate, and no anastomotic complications. Transparietopleural cholangiography demonstrated dilatation of the right intrahepatic biliary tract and diffuse stenosis affecting the common hepatic duct, hepatic hilum, and segmented biliary branches. External-internal percutaneous drainage of the biliary tract was performed 29 days postoperative.

After two days there was no obvious sign of improvement and the biochemical work up was as follows: BBT 19.6 mg/dl; Bdd 16.5 mg/dl; GGT 658 IU/l; ALP 951 IU/l; GOT 104 IU/l; and GPT 111 IU/l. Exploratory laparotomy was performed with no pathological findings which justified cholelithiasis. Intraoperative echography showed only enlargement of the biliary wall with no intraluminal obstructive findings. Immediate after surgery, because of suspicion of a basic inflammatory condition, treatment was begun with methylprednisolone 1 mg/kg/24 h intravenously. Once intake was tolerated, this treatment was reduced to 10 mg orally/24 h during the second month. The analytical follow up was excellent, with BBT reduced to 1.8 mg/dl, and the remaining biological parameters were normal. Similarly, the episode of bicipital tenosynovitis of the left shoulder evolved satisfactorily. The patient maintained treatment with methylprednisolone, 10 mg orally/24 h for 2 months, with clinical-radiological and analytical resolution of the cholestatic process (fig 1).

What is exceptional about this patient is the triggering of a severe autoimmune inflammatory response in the biliary system based on the presence of lymphoplasmacytic infiltration, coexistence with other
autoimmune processes (episode of tenosynovitis in the shoulder of our patient), and good response to steroids that would reveal an autoimmune aetio-pathogenesis. Our group would include the possibility of exclusive biliary tract involvement, as was the case with our patient, after the stress of surgery. Taniguchi and colleagues reported relapse of autoimmune pancreatitis after cephalic duodenopancreatectomy although they do not refer to alterations in the biliary tract. Toosi and colleagues reported the appearance in two of their patients of post-surgical sclerosing cholangitis although only after biopsy of the pancreatic head. The appearance of sclerosing cholangitis after duodenopancreatectomy has not been reported previously. The short period of biliary involvement and the progression maintained in the biliary involvement led us to suspect an inflammatory process similar to that of autoimmune pancreatitis.

Neither therapy nor its duration have been well defined, and this can be seen in the different regimens used by both for autoimmune pancreatitis and autoimmune pancreatocholangitis. Erkelens and colleagues used prednisolone 0.5–1 mg/kg/day, followed by maintenance doses for six months. Some patients also received, albeit exceptionally, azathioprine at 50 mg/day, and this was used temporarily until resolution of the biliary endoprosthesis process. The results were satisfactory, although no therapeutic protocol has been defined. This disparity in criteria is manifested in other studies, such as that of Toosi and colleagues, who used ursodeoxycholic acid at 750 mg/24 h with almost complete return to a normal clinical and radiological picture. Other authors, such as Kojima and colleagues, maintained treatment according to the clinical-radiological changes, using a loading dose of 40 mg/24 h, with maintenance doses of 5 mg/24 h. Taniguchi and colleagues used prednisolone at 30 mg/24 h for one month, followed by 5 mg/24 h for nine months with satisfactory evolution. Kamisawa and colleagues, on the other hand, used a loading dose of prednisolone of 30–40 mg/24 h and maintenance doses of 5 mg/24 h until clinical check-up. Based on the hypothesis of an excessive fibroellular inflammatory response in our patient, we started therapy with prednisolone 1 mg/kg for four weeks, with progressive reduction to 10 mg/24 h over the following four weeks. The maintenance dose was continued for a further two months, with analytical, radiological, and clinical resolution of the process.

**References**


**Calprotectin and IBD**

Costa and colleagues (Gut 2005;54:364–8) recently reported a study describing the ability of faecal calprotectin to predict relapse in the following year in patients with inflammatory bowel disease (IBD). They concluded that a calprotectin level >150 mg/l was predictive of relapse in Crohn’s disease (CD) and in ulcerative colitis (UC), but was not effective in predicting relapse in UC. Unfortunately, we believe that the authors failed to demonstrate these two points. If faecal calprotectin >150 mg/l was clearly predictive of relapse in UC patients, this was not the case in CD (p = 0.07 and p = 0.31 for the likelihood ratio test in univariate and multivariate analyses, respectively). This may be due to the method used to determine the cut off value for calprotectin. Firstly, the receiver operating curve (ROC) method did not provide any cut off value for CD as the curve was not different from the diagonal and the confidence interval of the area under the curve included 0.5 (0.40–0.77). Secondly, the ROC curve method was not appropriate as it does not take into account the time to relapse, in contrast with the proportional hazards model used to test the predictive value of calprotectin. Classical methods related to time to relapse should have been preferred.

The assertion, both in the title and in the text, that calprotectin was a stronger predictive marker of relapse in UC than in CD was not statistically tested by the authors. This assertion probably came from the high value for the hazard ratio in UC, compared with that in CD, but these values are misleading because of the exponential transformation of the coefficient in the proportional hazard model. When roughly calculating these coefficients and their standard error, the figures are much less convincing. In the univariate analysis the results are 1.39 (0.76) for CD and 2.35 (0.75) for UC, and the comparison between these two estimates gives a p value of 0.28 (p = 0.15 with estimates from the multivariate analysis). These disappointing results may be the consequence of a lack of power due to the relatively small number of patients.

Another important point is that the analysis was based on the assumption that the biomarker is able to predict relapse with the same strength whether the relapse occurs early after evaluation or later during follow up. If this is true it means that the calprotectin level is a characteristic of the
disease, including the whole 12 month follow up period. As discussed by the authors, calprotectin, as well as erythrocyte sedimentation rate (ESR) or C reactive protein (CRP), are probably markers of the degree of infra-clinical disease activity at the time of their measurement, and therefore can change with time in a given subject. To test this hypothesis, it should have been verified that their hazard ratios varied with time during follow up (the power of this analysis will however be limited).

Comparison of calprotectin with other classical predictive markers is also debatable. Indeed, cut off values for calprotectin were assessed using ROC curves, with some success for UC, and were three times higher than the upper limit of the normal range. In contrast, for ESR and CRP, the upper limits of the normal range were chosen as cut off values, following failure of the ROC curve method which was unfortunately not appropriate.

Finally, the authors stated that three variables were significant predictors of relapse—namely, calprotectin level, smoking habit, and UC activity index (UCAI) or CDAI—whereas only calprotectin and CDAI were found to be independently correlated to time to relapse in UC and CD, respectively. In conclusion, we agree with Pardi and colleagues’ that identification of biomarkers predictive of relapse could have important implications for the management of IBD patients, we are less convinced by the data presented. As acknowledged in the letter, the power of this analysis was however limited.

We disagree with Lemann and Mary if they wish to downplay the remarkable difference between the diagnostic groups. Firstly, we strongly disagree that a cut off value for calprotectin level >150 µg/g is predictive of relapse in CD and UC, but is more effective in predicting relapse in UC. For UC, and were three times higher than the upper limit of the normal range. In contrast, for ESR and CRP, the upper limits of the normal range were chosen as cut off values, following failure of the ROC curve method which was unfortunately not appropriate.

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