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LETTERS

Crohn's-like enterocolitis associated with mycophenolic acid treatment

In the European Crohn's and Colitis Organisation (ECCO) paper of 2006 (*Gut* 2006;**55**(Suppl 1):i1–15), consensus on the diagnosis of Crohn's disease was described. However, we were surprised that nothing was mentioned about the association between the use of mycophenolate mofetil (MMF, Cellcept) and the occurrence of Crohn's-like enterocolitis.

MMF is widely used to prevent rejection after solid organ transplantation. The active compound, mycophenolic acid (MPA), is a reversible, non-competitive inhibitor of inosine monophosphate dehydrogenase (IMPDH), the rate-limiting enzyme in de novo purine biosynthesis in T and B lymphocytes. The most common adverse drug reactions of MMF are gastro-intestinal complaints.[1–3] In 2003, a prospective cohort study including 26 renal transplant recipients with persistent diarrhoea showed for the first time that in patients using MMF, Crohn's-like enterocolitis could occur.[4] This condition was present in nine (35%) patients. Two years later, another follow-up study reported Crohn's-like changes in the colon mucosa in patients with diarrhoea in association with the use of MMF.[5]

In our centre recently, a kidney transplant patient treated with MMF presented with Crohn's-like enterocolitis. The patient was 57 years of age, and had received a renal transplant in 2001. In the first year post-transplant, she was treated with cyclosporine, prednisone and FTY720 (fingolimod, an immunosuppressant). One year after transplantation, FTY720 was discontinued and MMF therapy was started. Prednisone was stopped after 18 months. In 2003 her clinical course was complicated by breast cancer, for which she was treated with lumpectomy and post-operative radiotherapy. In 2004 and 2005 the MMF dose was reduced to 250 mg twice daily because of diarrhoea.

In November 2006, she complained of abdominal pain and anal mucus loss. A sigmoidoscopy showed several skiplesions of the colon descendens and sigmoid, and linear ulceration in the sigmoid colon (fig 1).

There was no inflammation in the rectum. The endoscopic picture was suggestive of Crohn's disease. Biopsies showed active colitis with epitheloid granulomas, compatible with Crohn's disease. The MMF dose was 250 mg twice daily, and MPA trough concentrations were between 0.4 and 1.0 mg/l.

Based on the assumption that this might be a manifestation of MMF-related enterocolitis, it was decided to discontinue MMF therapy, and switch to sirolimus as immunosuppressant to prevent rejection. Six weeks after discontinuation of MMF the abdominal pain and mucus loss gradually disappeared. A second sigmoidoscopy was performed in March 2007, and showed no more inflammation and ulcers. Histological examination of biopsies confirmed this recovery. An effect on enterocolitis has not been reported for sirolimus, leaving the discontinuation of MMF as the most likely explanation for our patient's recovery. The clear recovery of both symptoms and histology after discontinuation of the MMF therapy in our patient confirms our hypothesis.

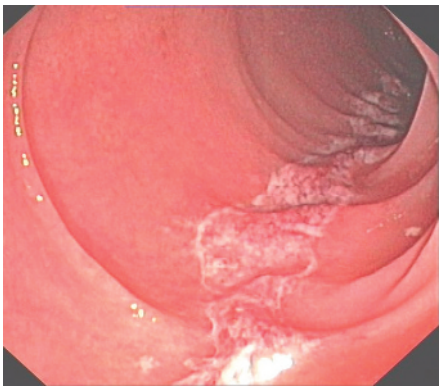

Figure 1 Linear ulcer in the sigmoid colon.

The pathophysiological mechanism for the histological changes during MMF therapy may be an effect of one of the metabolites of MPA, acyl glucuronide (AcMPAG). Acyl glucuronides in general are associated with drug toxicity and tissue damage, due to irreversible, covalent binding to plasma proteins, lipids and nucleic acids.[6 7] As a result of binding of the acyl glucuronide to protein molecules, this protein can be chemically modified and its function disturbed. Because chemically modified proteins can act as antigens, they can activate the immune system and cause an autoimmune response.[7]

In vitro studies have shown that AcMPAG induces the release of tumour necrosis factor α and interleukin 6.[6] These cytokines play a role in inflammatory disorders of the gut, like Crohn's disease.[6 8 9] Therefore, AcMPAG may be the association in the development of Crohn's-like enterocolitis during treatment with MMF.

Nephrologists and gastroenterologists should be aware that patients treated with MMF who show ulcerative inflammation in the small bowel or colon may have drug-induced enterocolitis. Discontinuation of the MMF therapy is then the approach of first choice, and may quickly lead to recovery, obviating the need for pharmacotherapy directed at Crohn's disease.

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Iron deficiency anaemia guidelines: time for an update?

Gregory *et al* recently discussed (*Gut* 2007;**56**:1319) the importance of appropriately investigating iron deficiency anaemia (IDA) in accordance with updated British Society of Gastroenterology (BSG) guidelines published in May 2005.[1] As part of an audit they found that 41% of their patients with a microcytic anaemia had ferritin levels measured. Those with a low ferritin level had subsequent gastro-intestinal investigations. We feel it is important to clarify that whilst serum ferritin has an important role in the evaluation of patients with anaemia, it should be remembered that it may be elevated as part of an acute phase response or in malignancy and hence is not always an accurate marker of iron deficiency in patients with a microcytic anaemia. Iron studies may provide additional information in this scenario. A normal ferritin in such circumstances should not preclude appropriate gastro-intestinal investigation.

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We would also like to highlight that the present BSG guidelines for the management of IDA focus upon endoscopic and barium investigation of the gastro-intestinal tract and do not incorporate guidance on those patients who may be unsuitable for these investigations. The diagnosis of significant gastro-intestinal pathology may therefore be delayed or potentially overlooked. In this clinical setting we would advocate the use of computed tomography (CT) imaging.

Two main CT methods are presently employed. The first is CT colonography (pneumocolon), which requires a laxative bowel preparation. Air or carbon dioxide is insufflated into the colon using a rectal tube. Multiple CT images are obtained with the patient in both supine and prone positions. The second is minimal preparation CT, which involves patients taking an oral contrast agent used for faecal tagging, with images taken in a supine position.

CT imaging should be considered for patients unable to undergo colonoscopy or barium enema due to frailty or reduced mobility, and in patients immediately after myocardial infarction in which endoscopy is contraindicated. Although abdominal CT may add prognostic information if significant pathology is identified, the co-morbidities present in these patients may limit the treatment options available. In our experience CT imaging of the colon or barium enema may also be preferable as an initial investigation in patients on warfarin for metallic heart valves. It prevents the need for hospitalisation for conversion of their warfarin to heparin for colonoscopy, which may result in delayed investigation and diagnosis of significant colonic pathology.

CT imaging carries several possible advantages over colonoscopy including a potentially shorter procedural time, fewer complications, more consistent evaluation of the entire colon, it does not require sedation and has the added benefit of detecting major extra-intestinal pathology in up to 23% of cases.[2] In our hospital we have identified three renal cell carcinomas, an atrial myxoma and thoracic aortic aneurysm whilst investigating IDA by CT. It also allows evaluation of the proximal colon in those with distal obstructing colonic lesions. The sensitivity of minimal preparation CT for the detection of colorectal cancer has been reported at 100%, with a specificity of 87%.[3]

The disadvantages of CT include the inability to biopsy the pathology detected, the exposure to radiation, and the detection of indeterminate findings that may require further assessment or follow-up imaging. Similar to colonoscopy, CT colonography may be limited by inadequate bowel preparation. There are also reduced detection rates of sub-centimetre lesions.[4] However, in the cohort of patients in which CT imaging is being considered, these factors are less relevant. The detection of significant colonic pathology may be the primary aim.

When the current BSG guidelines for the management of IDA are updated we recommend that abdominal CT be incorporated, for those patients who are unsuitable for endoscopic or barium investigation of the gastro-intestinal tract.[1]

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Narrow-band imaging and detection of colorectal adenoma

We have read the interesting article by Adler *et al* (*Gut* 2008;**57**:59–64) concerning the usefulness of narrow-band imaging (NBI) in the detection of colorectal adenoma. In their study, the authors showed that NBI significantly increased the number of polyps detected when compared with conventional white light colonoscopy. However, this difference was limited to those small hyperplastic polyps <10 mm. The result was not significant for adenoma. In addition, NBI can possibly induce a learning effect because the difference between NBI and conventional colonoscopy disappeared after 100 examinations.

A few questions arise in our mind after reading this paper. The detection rate for adenoma is exceptionally low in the early phase of a conventional group. Considering the average age of patients, experiences of endoscopists and various indications in a tertiary centre, the prevalence of adenoma was expected to be higher. The commonly quoted prevalence was 25% in men and 15% in women above the age of 50 years in screening colonoscopy. These figures were even used as criteria for quality colonoscopy.[1] The authors correctly pointed out that the adenoma rates vary widely in large colonoscopy trials. Ethnicity may be one of the possible reasons. In our experience with a Chinese population, the adenoma rate was 23.4% in a community hospital over a period of 6 years (unpublished data). However, this is not significantly different from Western experiences.

The authors stated that NBI may significantly increase hyperplastic polyp detection and impact on an endoscopist's workload. This brings back the question on whether small and diminutive polyps are clinically significant. More-recent studies showed that a significant proportion of these small and diminutive polyps are neoplastic adenoma. At least 4–10% of them harboured advance histology and a few of them were cancer.[2 3] Of the 1475 polyps <6 mm that we have removed over the past 6 years, 76.4% were adenoma and 9.1% were histologically advanced (two were cancers). Until long-term data from computed tomography colonography trials or convenient endoscopic method to distinguish neoplastic from non-neoplastic polyps are available, a clearing colonoscopy must be achieved to protect our patients from cancer development.

Although it was demonstrated in fig 1 in the paper by Adler *et al* that the detection rate for adenoma increased progressively for the conventional group, the authors did not mention how to differentiate an adenoma from other non-neoplastic polyps endoscopically with or without NBI. We cannot be sure whether this increase in adenoma detection rate can be attributed directly to the learning effect from NBI without knowing the learning process. We look forward to the authors' response to these questions.

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In vivo diagnosis of intestinal spirochaetosis by confocal endomicroscopy

We read with interest the article by Kiesslich *et al* (*Gut* 2006;**55**:591) on recent advances in confocal endomicroscopy, eg, in patients with collagenous colitis. Here we demonstrate that confocal endomicroscopy can be a useful tool to detect intestinal spirochaetosis in vivo.

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