Efficacy and strategy of pneumatic dilatation in achalasia

We read with interest the article by Eckardt et al reporting the long term results of pneumatic dilatation in achalasia (Gut 2004;53:629–33). Fifty four patients were followed up for a median of 14 years after a single pneumatic dilatation using the Browne-McHardy dilator. Five and 10 year remission rates were 40% and 36%, respectively, and repeated dilatations only mildly improved the clinical response. Most of the relapses occurred within one year of dilatation. Patients with post-dilatation lower oesophageal sphincter pressures of <10 mm Hg had a significantly better outcome. The authors suggest that failure to respond to the first dilatation should lead to consideration of alternative therapy.

We disagree with this conclusion and we would like to bring to your attention a recent prospective study on the long term effects of pneumatic dilatation in 11 patients with achalasia. A different approach was chosen—that is, treatment consisted of one or more pneumatic dilations under conscious sedation in order to achieve stable clinical remission, defined as persisting one year after the last dilatation. To this end, closer follow up was performed in the first year after dilatation (scheduled assessments at three and 12 months). Thereafter, clinical and manometric assessments were performed yearly for six years. The clinical score was according to Eckardt et al. Five patients needed one (30 mm diameter Rigiflex dilator) and six needed two (30 and 35 mm diameter) dilatations. No complications occurred. All patients remained in clinical remission and their lower oesophageal sphincter pressure decreased to <10 mm Hg and remained unchanged over time.

There are similarities in the results of the two studies if we take into account the outcome of our 11 patients in comparison with that of the eight patients of Eckardt et al with a lower oesophageal sphincter pressure of <10 mm Hg who had a remission rate of 73% after 6 years, and the observation that the six patients in our series who needed a second dilatation all relapsed within one year of the first dilatation agrees with the data by Eckardt et al, showing that most relapses occurred in the first 12 months. However, our dilatations were more successful and, importantly, a second dilatation led to a sustained remission in all patients. We do not know the reasons for this difference but we believe it may be at least partly related to our use of the non-compliant Rigiflex dilator, which is currently considered the best choice, although there are no adequately powered comparisons with the Browne-McHardy dilator in the literature. Similarly to our result, a recent paper has shown very good efficacy of a second dilatation with the Rigiflex dilator in patients who had relapsed. Another possible reason is the use of conscious sedation during the procedure which allowed us to complete all dilatations; Eckardt et al, who used topical anaesthesia only, had to prematurely terminate 17% of the procedures.

In conclusion, our published experience and our current clinical practice, involving treatment and follow up of 10–15 new achalasia patients each year, suggest that performance of one or two dilations until stable clinical results or remission is a valuable strategy, and that pneumatic dilatation under conscious sedation with the Rigiflex dilator is an effective long term treatment in most patients with achalasia.

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References

Authors’ reply
Penagini and Cantù should be congratulated for the remarkable results they were able to obtain in their patients with achalasia treated by pneumatic dilatation. To my knowledge, not a single study has so far produced similar results. A review of prospective studies in patients undergoing pneumatic dilatation with the Rigiflex dilator indicated that approximately 80% will have a good or excellent short term response. However, if such patients are observed for prolonged periods, the results obtained do not differ significantly from those observed following treatment with the older balloons. In a recent study, in which 56 patients were treated with the Rigiflex dilator and observed for more than 10 years, the long term success rate was 55%. This is in my opinion impressive because differences in treatments result are not so much related to differences in technique and operator experience but rather to the number of patients involved, duration of follow up, and finally the quality of the study design. It is hoped that carefully designed randomised studies, which are now in progress, will tell us whether we should continue to offer pneumatic dilatation to the great majority of patients with achalasia or whether we should advise them to undergo surgery instead.

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Probiotics in IBD: mucosal and systemic routes of administration may promote similar effects

We read with considerable interest the paper by Shell et al (Gut 2004;53:694–700) who reported the successful application of the subcutaneous route for probiotic attenuation of colitis.

We agree with the corresponding commentary of Ghosh et al (Gut 2004;53:620–2) regarding the need to study mechanisms underlying probiotic interactions. Recently, we further standardised a method to compare the anti-inflammatory potential of orally administered lactic acid bacteria (LAB) in a murine model of acute 2,4,6, trinitrobenzene sulphonic acid (TNBS) induced colitis. This model allowed us to discriminate “protective” strains, showing between 30% and 70% reduction of inflammatory score, from strains which did not significantly attenuate experimental colitis. We could select highly performing strains of Lactobacillus salivarius and Lactobacillus rhamnosus that consistently lowered colitis. In comparison, a strain of Lactobacillus acidophilus, Lactobacillus lactis, and Streptococcus gordoni never showed any improvement. For all five strains, we investigated the protective effect of a single intraperitoneal injection of 5 x107 live microorganisms, 24 hours prior to induction of colitis. Surprisingly, protection by the LAB strains via this systemic route closely matched the efficiency of the oral route (fig 1)

When evaluating both routes simulta-
neously, the anti-inflammatory effect was of comparable magnitude. Moreover, the pro-
phylactic impact of the intraperitoneal Lactobacillus salivarius strain was established up to two hours before TNBS administration. It is noteworthy that two delayed injections could lead to protection but caused marked weight loss (25% (p<0.05) v 15% and 11%, respectively, for control and oral route groups) with alleged fever.

Our findings clearly confirm those of Shell et al (Gut 2004;53:694–700) showing strain specific in vivo probiotic effects on the target tissue, suggesting a relationship between the type of LAB (or LAB components) and peritoneal immunocompetent cells. Pereyra and colleagues’ reported transient dose dependent induction of interferon in serum of intraperitoneal injected Lactobacillus bulgaricus while Streptococcus thermophilus did not. Recent
observations showed that heat treatment of an orally administered probiotic cocktail abolished the colitis protection in a DSS model, while irradiation improved it. Consequently, cellular integrity appears to be necessary to explain at least some part of the effect, although cell walls and peptido-glycans of killed bacteria cannot be considered as passive. Possibly both “good” and “bad” signals are given out by LAB, and the immune system is integrating all of them. Those “mixed” signals will no doubt be specific for each strain as well as dose dependent. Differences in physicochemical status could explain the mortality seen by Sheil et al., especially when using heat treated bacteria. Pereyra and colleagues established that the maximal non-lethal quantity of injected live LAB was $5 \times 10^7$ but it can be hypothesised that toxicity may also differ with strain and viability status. Both pro- and anti-inflammatory components of probiotics have been reported to interact with systemic immune cells, showing effects comparable to other well known anti-inflammatory or therapeutic molecules. It is therefore most probable that systemic delivery of specific live or killed probiotics may influence the delicate balance between Th1 and Th2 immunity, and subsequently have an impact on local immunity. Clear relationships, however, are not obvious. A first example is the case of subcutaneous CpG DNA that promoted a Th1 response and was able to alleviate some symptoms of DSS colitis but caused inflammation when administered after the onset of colitis. Second, different experimental models of colitis support a potential benefit of probiotic DNA, although it seems very premature to restrict this probiotic effect to nucleic acids only.

As emphasised by Gosh and colleagues (Gut 2004;53:620–2), approaches involving fractional studies are essential tools to complete the knowledge obtained from in vitro and ex vivo models and assist in understanding the interactions between LAB and the immune system. These studies may reveal common mechanisms active in inflammation, tolerance, and allergy models. Even if this study confirms the importance of the systemic route for certain probiotic activity, we cannot neglect the possible influence of local and innate immunity, the general status of the gut flora, and the role of epithelial cells in the cross talk between both.

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We are indebted to Danisco France for financial support.

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References


Mutations in anionic trypsinogen gene are not associated with tropical calcific pancreatitis
Pancreatitis is considered to be an autodigestive disease due to premature activation of trypsinogen inside the pancreas. Its genetic basis has recently been established with the identification of causal mutations in cationic trypsinogen gene (PRSS1) in patients with hereditary and non-hereditary pancreatitis. Mutations in other genes such as SPINK1 (encoding pancreatic secretory trypsin inhibitor) and cystic fibrosis transmembrane conductance regulator (CFTR) genes have also been associated with the disease. Tropical calcific pancreatitis is a type of idiopathic pancreatitis, reported particularly in the tropics. Recently, we and others demonstrated absence of PRSS1 mutations but significant prevalence of the N34S mutation in the SPINK1 gene in these patients. However, our study raised two important questions: firstly, the exact role of SPINK1 mutations in disease causation as catonic trypsinogen is normal with an intact autoysis site; and secondly, the cause of the disease in the remaining patients negative for both PRSS1 and SPINK1 mutations.

Of the nine members of the human trypsinogen gene family, only PRSS1, PRSS2, and PRSS3 are functional genes coding for cationic, anionic, and meso-trypsins, respectively. The remaining form accounts for about one third of the total trypsin in pancreatic juice. We investigated whether mutations in the anionic trypsinogen gene may contribute to the pathogenesis of tropical calcific pancreatitis. We screened exons 2 and 3 of the anionic trypsinogen gene in 68 well characterised Indian patients with tropical calcific pancreatitis. Subsequently, we also sequenced the promoter, complete coding region, and the flanking region in an attempt to look for any novel mutation.

Owing to the extremely high sequence homology between PRSS1 and PRSS2, a nested polymerase chain reaction (PCR) was used to ensure specificity. The primers were selected from the published study of Chen and colleagues and all of the exons of PRSS2 were PCR amplified, purified, and sequenced on both alleles using internal sequencing primers and the Big Dye terminator cycle sequencing approach. However, we did not find any of the reported or any novel mutations in the coding region or in the splice site junctions, except a synonymous polymorphism A90A (GCA>GGA) in exon 3 of the anionic trypsinogen gene. This variation was observed in both the heterozygous
and homozygous states with a mutant allele frequency of 0.58 (9 AA, 20 GG, and 39 AG) and was comparable with 0.61 in 50 controls. The frequency of 0.58 (9 AA, 20 GG, and 39 AG) in the pathogenesis of the disease. Screening for other genetic or non-genetic factors played a role in the tropical calcific pancreatitis and suggest a role for other genetic or non-genetic factors in the pathogenesis of the disease. Screening of genes such as CFTB may explain the disease in the remaining patients. It also affirms the importance of the N345 mutation in SPINK1 as the major genetic factor for this type of pancreatitis.

Elevated plasma protein C levels correlate with the presence of fatty liver (NASH and NAFLD)

The clinical implications of non-alcoholic fatty liver disease (NAFLD) are derived mostly from its common occurrence in the general population and the potential of the condition to progress to fibrosis and cirrhosis. Markers that help in making an early diagnosis and treatment warranted. Protein C is a vitamin K-dependent glycoprotein that functions as a circulating anticoagulant through proteolytic cleavage and inactivation of the coagulation factors Va and VIII. Whether protein C levels increase in patients with NAFLD has not been assessed.

We measured protein C levels in 44 patients (28 men and 16 women; mean ages 45 (11) and 49 (12) years, respectively; 15 patients with fatty liver (FL), 15 with non-alcoholic steatohepatitis (NASH), and 14 with chronic viral hepatitis B+ C (CH). All were diagnosed by histology and liver technetium scan or ultrasound. Ten healthy subjects were used as controls. Obesity, hyperlipidaemia, and diabetes were present in 60%, 73%, and 23% of cases, respectively; 64% of patients had elevated liver enzyme tests (alanine aminotransferase 45 (21) U/I in FL and 43 (18) U/I in NASH). Mean protein C levels were significantly increased in patients with NAFLD (n = 30) compared with those with chronic viral hepatitis (140 (36) vs. 101 (24); p < 0.0009) and healthy individuals (140 (36) vs. 120 (12); p < 0.04).

No significant difference in protein C levels was noted between simple fatty liver and NASH. (149 (34) and 130 (37), respectively; p = 0.97). A significant correlation was found between protein C and extent of inflammation (r = 0.63; p < 0.001) (fig 1), insulin resistance index (r = 0.3; p < 0.01), and triglyceride levels (r = 0.45, p < 0.001). Protein C could discriminate correctly between NAFLD and chronic viral hepatitis in 82% of cases. No significant association was found between protein C and aminotransferase levels.

In conclusion, protein C was elevated in patients with NAFLD. The underlying mechanism remains unknown. Ageeall et al. suggested an increase in hepatic synthesis of protein C due to increased hepatic insulin resistance. Increased levels have been reported in patients with diabetes, hypertriglyceridaemia, and nephrotic syndrome, with the use of anabolic steroids, oral contraceptives, and alcohol, and with increasing age. Diabetes and hypertriglyceridaemia are predisposing conditions to fatty liver and were present in 23% and 73% of cases, respectively. The remaining conditions were excluded by clinical and biochemical findings. Although more studies are needed, these preliminary findings suggest that elevated protein C levels together with elevated liver enzymes may be used as markers for NAFLD and may obviate the need for liver biopsy.
totally and patient No 4 partially colecto-
mised because of slow transit constipation. 
Patient No 6 was proctocolectomised due to 
refractory colitis. The patients were further 
investigated with magnetic resonance (MR) 
enterography and video capsule enteroscopy to 
establish whether there were any signs of 
IBD. If these examinations showed any 
pathology, push enteroscopy and ileocolo-
scopy were also performed. All biopsies 
collected over the years were re-evaluated. 

MR enterography did not reveal any 
pathological changes in any of the subjects. 
In three patients (Nos 1, 3, and 4), video 
capsule enteroscopy revealed Crohn-like 
ulcerations/erosions in the stomach and 
small intestine. Further examination of 
patient No 1 by push enteroscopy confirmed 
the erosions in the stomach and one third of 
the proximal small intestine. In patient No 3, 
capsule enteroscopy showed aphthous ulcers 
typical of Crohn’s disease throughout the 
distal jejunum and ileum (fig 1A). 
Ileocolonoscopy showed the same picture in 
the ileum and ileorectal anastomosis. 

Histopathological examination of the full 
thickness biopsies from patient Nos 1 and 2 
showed visceral degenerative neuropathy, 
combined with vaccination of the intesti-
 nal cells of Cajal (ICCs). In patient Nos 3 and 
6, lymphocytic ganglionitis was found in 
both neural plexa of the resected colon and 
ileum (fig 1B), with signs of neurone 
degeneration, and 50% and 80% reduction 
of ICCs in the perimyenteric ICC-plexus and 
deep muscular plexus of the circular muscle 
layer, respectively. Patient No 4 had a normal 
biopsy, and patient No 5 was not biopsied. 

Examination of mucosal biopsies from 
patient No 1 revealed focal active inflamma-
tion in the duodenum and caecum, and 
chronic inflammation in the rectum; patient 
No 5 had multifocal mild antral cryptitis, and 
both patients were diagnosed with suspected 
Crohn’s disease. Colon biopsies from patient 
No 6 revealed epithelioid cell granulomas and 
multinucleated giant cells, as well as multi-
focal transmural lymphoid hyperplasia con-
sistent with Crohn’s disease. 

In three patients (Nos 1, 3, and 4), dysmotility preceded the mucosal changes. 
In patient Nos 2 and 5, these two entities occurred simultaneously, while in patient No 6, 
dysmotility developed after proctococe-
tomy. Ganglionitis in patient No 3 could have been caused by Crohn’s disease before 
other symptoms of the disease developed. 
Treatment with 5-ASA has reduced her 
abdominal pain. The normal histology of 
the sigmoidum in patient No 4 does not 
exclude the possibility of ganglionitis in other parts of the bowel due to the known patchy 
involvement of the gut in Crohn’s disease. 
The present observations indicate that 
apart from inflammation, even purely deg-
erative neuronal and ICCs changes seen in 
CIP can occur in patients who also have IBD/ 
an IBD-like condition. At present, it is not 
known whether the observed abnormalities 
are part of IBD or independent of each other. 
This small patient sample prevents us from 
drawing any definite conclusion regarding 
this question. Further observations are 
needed to establish whether or not this 
connection is causal.

Table 1 Summary of the findings in our patients

<table>
<thead>
<tr>
<th>Patient No:</th>
<th>Debute age/CIIP age (y)</th>
<th>Main symptoms</th>
<th>Clinical diagnosis</th>
<th>Endoscopic pathology</th>
<th>Histopathology</th>
<th>Antroduodenal manometry</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 23/F</td>
<td>16/22</td>
<td>Pain, bloody diarrhoea</td>
<td>Crohn’s disease, CIIP</td>
<td>Small and large bowel</td>
<td>Degenerative neuropathy</td>
<td>Suspected Crohn’s disease</td>
</tr>
<tr>
<td>2 26/F</td>
<td>15/25</td>
<td>Pain, vomiting</td>
<td>Prolitits, CIIP</td>
<td>Rectum</td>
<td>Degenerative neuropathy</td>
<td>Abnormal</td>
</tr>
<tr>
<td>3 35/F</td>
<td>35/39</td>
<td>Constipation, dyspepsia</td>
<td>Crohn’s disease, CIIP</td>
<td>Small and large bowel</td>
<td>Gangliolitis</td>
<td>Normal</td>
</tr>
<tr>
<td>4 44/F</td>
<td></td>
<td>Constipation, pain</td>
<td>Suspected Crohn’s disease, CIIP</td>
<td>Small bowel</td>
<td>Normal</td>
<td>Abnormal</td>
</tr>
<tr>
<td>5 55/M</td>
<td>39/41</td>
<td>GORD, later pain and diarrhoea</td>
<td>Suspected Crohn’s disease, CIIP</td>
<td>Normal</td>
<td>Suspected Crohn’s disease</td>
<td>Abnormal</td>
</tr>
<tr>
<td>6 67/M</td>
<td>61/64</td>
<td>Pain, weight loss</td>
<td>Crohn’s disease, CIIP</td>
<td>Large bowel</td>
<td>Gangliolitis, Crohn’s disease</td>
<td></td>
</tr>
</tbody>
</table>

CIIP, Chronic idiopathic intestinal pseudo-obstruction; GORD, gastro-oesophageal reflux disease.

Figure 1 Patient No 3. (A) Capsule endoscopic view of the terminal ileum showing an aphthous ulceration in the ileum. 
(B) Moderate lymphocytic infiltrate around and within the myenteric ganglia (haematoxylin-eosin x100).

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Cannabinoid hyperemesis: not just a problem in Adelaide Hills

We read the article by Allen and colleagues (Gut 2004;53:1566–70) with interest and would like to report a case of probable cannabinoid hyperemesis seen in a district general hospital in the UK.

A 21 year old chef was admitted to our hospital on seven occasions over a two year period (April 2001 to December 2002) with profuse vomiting. Apart from a history of migraine as a child, he was fit and well. He smoked cannabis. Physical examination was unremarkable. The observation that the patient wanted to take regular baths because he had found that bathing eased the sickness was documented in the nursing notes but its significance was not appreciated. Investigations during attacks disclosed neutrophilia but blood urea, electrolytes, liver biochemistry, and serum amylase were normal. Abdominal x ray was also normal. Upper gastrointestinal endoscopy showed grade 1 oesophagitis and gastritis. Gastric biopsies were histologically normal. An abdominal ultrasound scan and small bowel barium follow through examination were normal. Additional normal or negative investigations included: autoantibodies and immunoglobulins, C reactive protein, and urinary porphyrin screen. Computed tomography scan of the brain was also normal.

During his last admission, the patient’s girlfriend showed us an article published in an Australian newsletter which she had obtained via the internet, in which Dr JH Allen had raised the possibility of a link between recurrent vomiting and cannabis abuse. With the aid of the internet we traced and contacted Dr Allen who shared his experience of this condition with us.

Reviewing the patient’s history, he freely admitted to smoking cannabis and experiencing the compulsive desire to bathe during bouts of vomiting. Following his last admission in December 2002, our patient stopped smoking cannabis and has remained free of symptoms. This clinical presentation was almost identical to the cases described by Allen et al, together with the response to cessation of smoking cannabis, supports the view that our patient was suffering from cannabinoid hyperemesis and that this condition is international.

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Inflammatory bowel disease stimulates formation of carcinogenic N-nitroso compounds

In patients with inflammatory bowel disease (IBD) there is an increased incidence of colorectal cancer is observed. Although severe inflammatory conditions per se represent a risk factor for neoplasia, we would like to draw attention to the possible role of increased activity of inducible nitric oxide synthase (iNOS), as found in IBD patients, in the endogenous formation of carcinogenic N-nitroso compounds (NOC). In healthy individuals, relatively small amounts of NOC are formed by the interaction between NOC precursors (NOCP), present in dietary items such as meat and fish, and nitrosating agents derived from dietary nitrate. It has been proposed that endogenous formation of NOC may explain the link between meat consumption and colon cancer risk found in epidemiological studies. We hypothesised that as a result of chronic inflammatory conditions in the large intestine, increased colonic iNOS activity may produce an excess of NO, nitrogen oxides, and nitrite, which in turn react with NOCP present in the colon to produce relatively high levels of NOC. Increased formation of NOC in IBD patients may thus contribute to the relatively high incidence of colorectal cancer associated with this disease.

A recent population based case control study showed that, in cases with a history of IBD, increased exposure to drinking water nitrate was associated with an increased risk of colon cancer whereas no such association was found in the overall population. This clearly indicates that the risk of colon cancer in IBD patients is not only determined by the disease itself but dietary factors known to influence the endogenous formation of NOC are also associated with an increased risk in these patients. Although both the increased formation of NOC found in mice with chemically induced colitis and increased levels of NO and nitrite found in the colonic lumen of patients with ulcerative colitis support this hypothesis, we believe that NOC levels have never been investigated in IBD patients.

Therefore, we collected faecal samples from 17 patients diagnosed with ulcerative colitis and 17 healthy controls, and determined levels of N-nitrosodimethylamine (NDMA), a predominant carcinogenic NOC, using gas chromatography-mass spectrometry, as previously described. The study was approved by the medical ethics committee of the Maasland Hospital, Sittard, the Netherlands, and all patients gave their consent. In 41% of patients, we found levels of NDMA above the detection limit of 1 ng/g faeces, compared with 35% of controls. Comparison of concentrations in NDMA positive samples showed that the average concentration in patients was significantly higher than that in the control group (table 1). When IBD patients were subdivided into hospitalised and non-hospitalised cases, the difference between the non-hospitalised group and controls was even more pronounced, whereas NDMA concentrations in hospitalised patients and controls were comparable. As all hospitalised patients received only liquid nutrition (Nutrison; Nutricia, UK) without additional intake of NOCP rich dietary foods, these results confirm that the combination of high dietary NOCP intake and inflammation may present a risk factor.

Most research on endogenous NOC exposure has focused predominantly on the

Table 1 Faecal N-nitrosodimethylamine (NDMA) concentrations in patients with inflammatory bowel disease (IBD) and in healthy controls

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>All IBD cases (n = 17)</th>
<th>Non-hospitalised cases (n = 10)</th>
<th>Hospitalised cases (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>%NDMA positive</td>
<td>35</td>
<td>41</td>
<td>56</td>
<td>25</td>
</tr>
<tr>
<td>NDMA (ng/g)*</td>
<td>1.4</td>
<td>10.9†</td>
<td>14.3†</td>
<td>2.4†</td>
</tr>
</tbody>
</table>

*Average concentration of NDMA positive samples.

†p<0.05, ††p<0.01: significantly higher compared with the control group (Mann-Whitney U test).

†p<0.05: significantly lower compared with non hospitalised cases (Mann-Whitney U test).

Conflict of interest: None declared.

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Hepatocellular carcinoma occurring after successful treatment of childhood cancer with high dose chemotherapy and radiation

Hepatocellular carcinoma (HCC) is one of the world’s most common malignancies and accounts for more than 90% of all primary liver cancers. A number of different risk factors have been identified for the development of HCC.1 Hepatitis B carrier state, environmental toxins, chronic hepatitis C virus infection, hereditary haemochromatosis, and liver cirrhosis of almost any cause are well known risk factors for HCC. In addition, environmental toxins such as aflatoxins and contaminated drinking water may contribute to the pathogenesis of HCC, especially in Asia and underdeveloped countries. Finally, a number of HCC cases have occurred after the use of thorotrast for diagnostic procedures, and survivors of the atomic bomb of Hiroshima were also at higher risk for HCC development, indicating that radiation might also induce the development of HCC. Herein we describe a rare case of HCC occurring in a patient 17 years after successful treatment of peripheral neuroectodermal tumour (PNET).

A 32 year old female presented with pain in the right upper quadrant of her abdomen. Seventeen years prior to presentation in our hospital this patient was treated for a PNET with a combination of high dose chemotherapy (vincristine, adriablastin, ifosfamide, and actinomycin D) and surgical removal of the 10 x 5 cm tumour from her right chest followed by combined radiation (60 Gy) and chemotherapy. There were no signs of any recurrence of the tumour observed on her last check up 12 month earlier. Physical examination of the patient in our clinic showed typical signs of late radiation damage (erythema of the skin and an underdeveloped right breast) (fig 1). A firm 3-5 cm mass was palpable at the lower edge of the liver. Laboratory tests showed elevated alpha-fetoprotein (41881 μg/l). Hepatitis serology was negative and there was no evidence of any other liver disease. Magnetic resonance imaging revealed multiple intrahepatic masses up to 6.5 cm. A biopsy from the hepatic tumour was taken and confirmed the clinical diagnosis of HCC. The patient died three months after the diagnosis was made.

To the best of our knowledge, secondary HCC following high dose chemotherapy has never been described and therefore we searched the German Childhood Cancer Registry, which started to register all cases of malignancies in children (<15 years) in 1980. This database also collects data from secondary malignancies following chemotherapy. In this database we were able to detect a total of four more cases of secondary HCC, which are summarised in table 1. Interestingly one patient was hepatitis B surface antigen positive.

Radiotheraphy has been shown to be associated with an increased risk of solid tumours 10–15 years after treatment and later.3 There is one report in the literature of a radiation induced hepatoma in a patient with a non-malignant haemangiomatisa, which occurred 20 years after radiation of the liver with 28.5 Gy. To date, the molecular mechanism of hepatocarcinogenesis is not completely understood. The main causative agents—hepatitis B virus, hepatitis C virus, and aflatoxin B1—have been identified, which together are responsible for approximately 80% of all HCC in humans. This series of cases clearly supports the notion that secondary HCC can follow not only radiation therapy of children but also high dose chemotheraphy, and may prompt careful follow up examinations of the liver in patients with a possible risk for the development of HCC.

Table 1 Details of five cases of secondary hepatocellular carcinoma

<table>
<thead>
<tr>
<th>First malignancy</th>
<th>Age (y)</th>
<th>Treatment</th>
<th>Age when HCC was diagnosed (y)</th>
<th>Time from first to second malignancy (y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALL</td>
<td>4</td>
<td>CTx</td>
<td>20</td>
<td>15</td>
</tr>
<tr>
<td>Osteosarcoma</td>
<td>4</td>
<td>CTx, RTx</td>
<td>18</td>
<td>9</td>
</tr>
<tr>
<td>ALL</td>
<td>4</td>
<td>na</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>PNET</td>
<td>15</td>
<td>CTx, RTx</td>
<td>33</td>
<td>18</td>
</tr>
<tr>
<td>Teratoma</td>
<td>2</td>
<td>na</td>
<td>19</td>
<td>16</td>
</tr>
</tbody>
</table>

ALL, acute lymphocytic leukaemia; PNET, peripheral neuroectodermal tumour; CTx, chemotherapy; RTx, radiation therapy.

*This patient was hepatitis B surface antigen positive.

Biologics in inflammatory disease: infliximab associated risk of lymphoma development

In their excellent overview of currently available biologic compounds that are in use or under investigation for Crohn’s disease (CD), Sandborn and Faubion (Gut 2004;53:1366–73) reconfirm the unique standing of infliximab. They also note the ongoing discussion concerning the increased occurrence of lymphoproliferative disorders in patients who received infliximab.

Recently, we followed a 61 year old patient with a 31 year history of relapsing CD. Initial treatment was with steroids but after 10 years of use the patient was switched to azathioprin and infliximab. Two years later, infliximab was added 22 months before the current admission. Total infliximab therapy included three doses of 400 mg (5 mg/kg) within two months and resulted in a marked reduction of CD activity (azathioprin was maintained). On admission 10 months after the last infliximab infusion, the patient relapsed again with ulcerations and multiple rectovaginal fistulas. Biopsies showed a polymorphous tumour infiltrate. Tumour cells were positive for CD30 and negative for T and B cell markers as well as the anaaplastic large cell lymphoma kinase (ALK) and Epstein-Barr virus (EBV) associated proteins. A multiplex polymerase chain reaction approach revealed a clonal T cell population and an oligoclonal B cell population. Based on these results, the diagnosis was ALK negative anaplastic large cell lymphoma with null/T cell phenotype. Clinical stage was IAE. CHOP-chemotherapy resulted in complete clinical and histological remission, which was evidenced by computer tomography, positron emission tomography, and negative rectal histology. Polymerase chain reaction analysis of the rectal biopsies revealed no T cell receptor gene rearrangement.

Three months later, the patient presented with postobstructive pneumonia. Transbronchial biopsies showed a diffuse large B cell lymphoma. In contrast with the preceding rectal biopsies, bronchial tumour cells were positive for CD20, EBER, EBNA2, and LMP-1, indicating EBV infection of latency type III, were detected in tumour cells.
However, tumour cells were negative for CD30 and ALK protein. Molecular analysis demonstrated a monoclonal immunoglobulin heavy chain rearrangement in the absence of a T cell receptor rearrangement, confirming the diagnosis. The tumour was neither heavy chain rearrangement in the absence of non-Hodgkin’s lymphoma of 6.6/100 000 treated patients. This series was compared with 111 age and sex matched controls. The research protocol had been treated with infliximab for Crohn’s disease: the Mayo Clinic experience in 500 patients. Gastroenterology 2004;126:19–31.


Genotypes 677TT and 677CT+1298AC of methylenetetrahydrofolate reductase are associated with the severity of ulcerative colitis in central China

Increased blood levels of homocysteine have been found to be associated with inflammatory bowel disease (IBD) in several studies. The main genetic determinant associated with elevated plasma levels of homocysteine (t-Heys) is the MTHFR 677CT→T gene polymorphism of methylenetetrahydrofolate reductase, a critical enzyme involved in the remethylation pathway of homocysteine. An association of the MTHFR 677T allele with IBD has been reported in Northern Europe but not in three series from Italy and France. Double heterozygosity MTHFR 677CT+1298AC also produces reduced enzyme activity and increased t-Heys, but its association with IBD has never been studied. Similarly, the association of IBD with transcobalamin (TCN1 776G→C), a genetic determinant that influences transcobalamin levels and t-Heys, is not known. Transcobalamin is the protein that promotes intestinal transcytosis and cell delivery of vitamin B12, the cofactor of the methionine synthase dependent remethylation pathway.

In this study, we have evaluated the association of ulcerative colitis (UC) with MTHFR 677CT→T, MTHFR 1298A→C, and TCN1 776G→C in a series of 72 patients from central China who gave informed consent. This series was compared with 111 age and sex matched controls. The research protocol was approved by the local appointed committee. Extraction of DNA and determination of polymorphisms were performed as described previously by us. A continuity corrected χ²-test and an ANOVA test were used, respectively, to assess differences in categorical and continuous variables between groups. Odds ratios of independent categorical variables...
Table 1: Clinical characteristics and methylenetetrahydrofolate reductase (MTHFR) and transcobalamin (TCN) polymorphisms in 72 patients with ulcerative colitis (UC) and 111 controls from central China

<table>
<thead>
<tr>
<th>Allele</th>
<th>ULC (n, %)</th>
<th>Controls (n, %)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTHFR 677T</td>
<td>44 (60.0)</td>
<td>81 (73.0)</td>
<td>0.0487</td>
</tr>
<tr>
<td>MTHFR 677C</td>
<td>28 (36.3)</td>
<td>30 (27.1)</td>
<td>0.0837</td>
</tr>
<tr>
<td>TCN 776G</td>
<td>62 (83.3)</td>
<td>102 (92.0)</td>
<td>0.0487</td>
</tr>
<tr>
<td>TCN 776G</td>
<td>14 (18.9)</td>
<td>29 (26.3)</td>
<td>0.0487</td>
</tr>
</tbody>
</table>

In conclusion, our study showed that the genotypes of MTHFR associated with a decrease in enzyme activity, seemed to be more significantly associated with extension of disease than with the primary risk, at least in central China.

References


CORRECTION
doi: 10.1136/gut.2004.045294corr1

The original article by Cosnes et al (Impact of the increasing use of immunosuppressants in Crohn’s disease on the need for intestinal surgery. Gut 2005;54:237–41), published in the February 2005 issue was incomplete. Figure 2 was missing from the proof. A corrected version of the pdf can be viewed at http://gut.bmjournals.com/cgi/data/54/2/237/DC1/1, and the missing figure can be seen here.
Coexistent chronic idiopathic intestinal pseudo obstruction and inflammatory bowel disease

B Ohlsson, F-T Fork, B Veress and E Toth

*Gut* 2005 54: 729-730
doi: 10.1136/gut.2004.058826

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