negative MCL were clinically similar to those with cyclin D1 positive MCL. The immunoreactivity for cyclin D2 in our reported case remains to be examined. Final confirmation for cyclin D2 or D3 in these patients with cyclin D1 negative MCL will be carried out in future studies.

A literature search using Japana Centra Revuo Medicina (in Japanese) (keywords: ulcerative colitis, mantle cell lymphoma; retrieval period: 1983–2007) found no cases, and a similar search in Medline (keywords: ulcerative colitis, mantle cell lymphoma) found only one case worldwide of colonic MCL with ulcerative colitis.[3] Therefore we consider this to be the second reported case to date of colonic MCL with ulcerative colitis. In the case reported by Dr Sinharay, the biopsied samples from pseudopolyps with active ulcerative colitis indicated an overexpression of cyclin-D1 protein, and a diagnosis of colonic MCL was made. The samples revealed multiple lymphomatous polyposis arising from a background of ulcerative colitis. However, it should be clarified whether the colonic MCL with multiple lymphomatous polyposis was primary or whether the patient developed MCL on a background of long standing ulcerative colitis, as described above.

Loftus *et al* (reference 2 in Dr Sinharay's letter) reported that the risk of developing NHL in ulcerative colitis does not exceed that of the general population. Dr Sinharay said that the possibility of ulcerative colitis transforming into NHL should be considered. We disagree, however, because the incidence is low. A definite correlation between ulcerative colitis and colonic lymphoma has not been reported, though it should be noted that colonic lymphoma can develop in cases of ulcerative colitis.

Immune modifier therapy involving an anti-CD20 antibody (rituximab) could be implicated in a small percentage of lymphoma patients, occurring in the setting of inflammatory bowel disease as described by Loftus *et al*. However, a multicentre phase II pilot study indicated that rituximab following induction chemoimmunotherapy appeared to prolong progression-free survival in various types of MCL without increasing toxicity, and is not limited to gastrointestinal lymphoma.[4] Forstpointner *et al* have also reported that maintenance therapy with rituximab was effective after salvage therapy with rituximab along with traditional chemotherapy, and significantly prolonged the response duration in patients with follicular lymphoma and MCL.[5] Furthermore, Ritchie *et al* have reported that combination therapy with hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) plus rituximab increases event-free survival in patients with previously untreated MCL.[6] Very recently Herold *et al* reported that rituximab added to first line mitoxantrone, chlorambucil, and prednisolone chemotherapy, followed by interferon maintenance, prolongs survival in patients with advanced follicular lymphoma.[7] We strongly suspect that immune modifier treatment involving rituximab added to traditional chemotherapy will produce more significant prolongation of progression-free survival. We look forward to future prospective studies of these important subjects.

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References

1 **Rosenwald A**, Wright G, Wiestner A, *et al*. The proliferation gene expression signature is a quantitative integrator of oncogenic events that predicts survival in mantle cell lymphoma. *Cancer cell* 2003;**3**:185–97.
2 **Fu K**, Weisenburger DD, Greiner TC, *et al*. Cyclin D1-negative mantle cell lymphoma: a clinicopathologic study based on gene expression profiling. *Blood* 2005;**106**:4315–21.
3 **Robert ME**, Kuo FC, Longtine JA, *et al*. Diffuse colonic mantle cell lymphoma in a patient with presumed ulcerative colitis: detection of a precursor monoclonal lymphoid population using polymerase chain reaction and immunohistochemistry. *Am J Surg Pathol* 1996;**20**:1024–31.
4 **Kahl BS**, Longo WL, Eickhoff JC, *et al*. Maintenance rituximab following induction chemotherapy may prolong progression-free survival in mantle cell lymphoma: a pilot study from the Wisconsin Oncology Network. *Ann Oncol* 2006;**17**:1418–23.
5 **Forstpointner R**, Unterhalt M, Dreyling M, *et al*. Maintenance therapy with rituximab leads to a significant prolongation of response duration after salvage therapy with a combination of rituximab, fludarabine, cyclophosphamide, and mitoxantrone (R-FCM) in patients with recurring and refractory follicular and mantle cell lymphomas: results of a prospective randomized study of the German Low Grade Lymphoma Study Group (GLSG). *Blood* 2006;**108**:4003–8.
6 **Ritchie DS**, Seymour JF, Grigg AP, *et al*. The hyper-CVAD-rituximab chemotherapy programme followed by high-dose busulfan, melphalan and autologous stem cell transplantation produces excellent event-free survival in patients with previously untreated mantle cell lymphoma. *Ann Hematol* 2007;**86**:101–5.
7 **Herold M**, Haas A, Srock S, *et al*. Rituximab added to first-line mitoxantrone, chlorambucil, and prednisolone chemotherapy followed by interferon maintenance prolongs survival in patients with advanced follicular lymphoma: an East German Study Group hematology and oncology study. *J Clin Oncol*, published Online First 9 April 2007. doi: 10, 1120/JCO.2006.06., 4618.

Does hyperhomocysteinaemia contribute to gastric carcinogenesis in *Helicobacter pylori* infected patients?

In a recent issue of *Gut*, Marino *et al* showed that eradication of *Helicobacter pylori* resulted in increased levels of vitamin B-12 (cobalamin) and decreased levels of plasma homocysteine in elderly patients (*Gut* 2007;**56**:469–74), confirming preliminary reports.[1] The authors recall that cobalamin deficiency is associated with *H pylori* infection and is a major cause of hyperhomocysteinaemia in the general population.

Global DNA hypomethylation, which is associated with hyperhomocysteinaemia,[2] is an epigenetic event often found in tumour cells.[3] The homocysteine raising effect of *H pylori* may thus promote gastric carcinogenesis. Consistently, a recent study showed that hyperhomocysteinaemia may increase the risk of developing gastric cancer in a Chinese population.[4] Along with Marino's results, these findings may provide new insights in our understanding of *H pylori* related gastric carcinogenesis.

One question remains open: Is eradication of *H pylori* the best way to prevent gastric cancer? The conclusion of the Maastricht III consensus report was that ''Eradication of *H pylori* infection has the potential to reduce the risk of gastric cancer development''.[5] Indeed, current evidence is insufficient to accurately identify a definitive population where prevention or treatment strategies have to be targeted. In this regard, future trials to identify high risk individuals for gastric cancer are eagerly awaited.[6]

Collectively, the above findings suggest that prevention strategies might target a subset of patients with lowest serum cobalamin levels. One question thus arises: Should we screen and treat *H pylori* positive patients for cobalamin deficiency (and hyperhomocysteinaemia) to reduce the risk of gastric cancer?

Future epidemiological and intervention studies assessing the influence of eradication of *H pylori* on the risk of gastric cancer must include the measurement of cobalamin and plasma homocysteine concentrations. This may shed new light on the *H pylori* story.[7]

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References

1 **Ozer B**, Serin E, Gumurdulu Y, *et al*. Helicobacter pylori eradication lowers serum homocysteine level in patients without gastric atrophy. *World J Gastroenterol* 2005;**11**:2764–7.
2 **Friso S**, Choi SW, Girelli D, *et al*. A common mutation in the 5,10-methylenetetrahydrofolate reductase gene affects genomic DNA methylation through an interaction with folate status. *Proc Natl Acad Sci USA* 2002;**99**:5606–11.
3 **Goelz SE**, Vogelstein B, Hamilton SR, *et al*. Hypomethylation of DNA from benign and malignant human colon neoplasms. *Science* 1985;**228**:187–90.
4 **Wang L**, Ke Q, Chen W, *et al*. Polymorphisms of MTHFD, plasma homocysteine levels, and risk of gastric cancer in a high-risk Chinese population. *Clin Cancer Res* 2007;**13**:2526–32.
5 **Malfertheiner P**, Megraud F, O'morain C, *et al*. Current concepts in the management of Helicobacter pylori infection – the Maastricht III Consensus Report. *Gut* 2007;**56**:772–81.
6 **Fuccio L**, Zagari RM, Minardi ME, *et al*. Systematic review: Helicobacter pylori eradication for the prevention of gastric cancer. *Aliment Pharmacol Ther* 2007;**25**:133–41.
7 **Pincock S**. Nobel Prize winners Robin Warren and Barry Marshall. *Lancet* 2005;**366**:1429.

Author's reply

We thank Dr Peyrin-Biroulet for his comments on our study and we would like to make some further observations. It is well accepted that *H pylori* is a group 1 carcinogen. The mechanisms whereby the microorganism induces gastric carcinogenesis are not completely understood but are linked to bacterial virulence factors, host genetics, and environmental factors. In human gastric carcinogenesis,