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Complete response in a patient with colonic mantle cell lymphoma with multiple lymphomatous polyposis treated with combination chemotherapy using anti-CD20 antibody and cladribine

A 59-year-old woman suspected of having colonic malignant lymphoma was transferred to our hospital (Japan Labour Health and Welfare Organization Tsubame Rosai Hospital, Tsubame, Niigata, Japan) in October 2003. Systemic CT scan showed no swollen lymph nodes. Gallium scintiscan useful in localising lymphoma, showed no abnormal accumulation. Endoscopic findings of the oesophagogastroduodenal tract showed no tumour lesions. Colonoscopic examination was performed in November 2003, and clearly revealed multiple small elevations (fig 1A). Endoscopic mucosal resections were performed on lesions and the resected specimens suggested mantle cell lymphoma (MCL). A second colonoscopic

examination performed in July 2004 revealed increased numbers of polyps, indicating a case of multiple lymphomatous polyposis (MLP). Biopsy was performed again to confirm the diagnosis of colonic MCL. Figure 1B–D shows the histopathological findings of both resected and biopsy specimens. Immunohistochemical examination of these specimens revealed positive immunoreactivity for CD20 and CD5 (fig 1E), and negative immunoreactivity for UCHL-1, CD10 and cyclin-D1. The patient was treated with combination therapy of an anti-CD20 antibody (rituximab) and 2-CdA (cladribine). (570 mg/day of rituximab was given intravenously on day 14 and 5.6 mg/day of cladribine was given intravenously from days 1 to 3.) After two courses of combination therapy, colonoscopic examination revealed that polypoid lesions had disappeared and complete response was obtained. In all, the patient underwent four courses of combination therapy and was then carefully followed up as an outpatient.

In the West, MLP is commonly considered to be a representation of MCL.¹ However, in

Figure 1 (A) Colonoscopic findings on 4 November 2003 showed multiple small elevations with a normal vessel pattern and erosions on the tops, from the ascending to descending colon. (B) A low-power histological picture of the specimen resected at the first colonoscopic examination on 4 November 2003 showing distinct, poorly circumscribed lymphoid follicles and the infiltration of lymphoma cells into the submucosal lesion of the colonic wall. The lesions were covered with normal mucosa (H&E stain). (C) High-power view showing diffuse proliferation of many small centrocyte-like cells (H&E stain). (D) High-power histopathological view of the biopsy specimens taken during the second colonoscopic examination in July 2004 showing lymphoepithelial lesion (H&E stain). (E) Immunohistochemical examination was shown to be positive for CD5.

Japan, cases of MCL with MLP are rare. Nasu *et al*² and Tateishi *et al*³ have reported on the reasons why differences exist between Western and Japanese views of the occurrence of MLP. They suggest that further discussion is needed on (1) why the pathological appearance of gastrointestinal MLP differs between primary gastrointestinal MCL and primary nodal MCL with invasion of gastrointestinal tract; (2) why Japanese and Western definitions of pathological diagnosis of malignant lymphomas differ; and (3) the differences in physiology between patients in Japan and in the West. MCL is characterised by positive immunoreactivity for CD5 and cyclin-D1 and negative immunoreactivity for CD10. Conversely, about 10% of cases with confirmed pathological diagnosis as MCL showed no cyclin-D1 overexpression.⁴ We considered this to be a case of MCL. Yatabe *et al*⁵ claimed that cases with positive immunoreactivity for cyclin-D1 showed true MCL, and that cases showing negative immunoreactivity for cyclin-D1 should be included among lymphoma cases with low-grade malignancy as low-grade MCL-like B cell lymphoma. As this patient showed negative immunoreactivity for cyclin-D1, has an indolent clinical course and resulted in a complete response, it may be considered among the cases that Yatabe *et al* identified as having a relatively positive prognosis. Nonetheless, MCL has commonly been resistant to classic chemotherapy. Recently, however, patients with MCL treated with a variety of new combination chemotherapies involving rituximab have shown high response rates⁶ and prolongation of progression-free survival.⁷ Additionally, other recent studies have found 2-CdA (cladribine) to be effective for a variety of indolent B cell lymphomas as the new purine analogues; the trial of this agent was moderately effective in the treatment of MCL.⁸ A literature search using Japana Centra Revuo Medicina and Medline found only two patients^{9,10} effectively treated with anti-CD20 antibody (rituximab) for gastrointestinal MCL. This is the first reported case to date in which a complete response was obtained by combination chemotherapy with anti-CD20 antibody (rituximab) for colonic MCL associated with MLP. Our findings suggest that combination therapy with anti-CD20 antibody and 2-CdA is appropriate for indolent B cell lymphoma of the gastrointestinal tract as colonic MCL. Further research on the most appropriate treatments for gastrointestinal MCL is needed.

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Response from the hornet's nest: furthering the debate on transplantation for alcoholic liver disease

O'Grady's leading article highlighted the ongoing debate surrounding liver transplantation for alcoholic liver disease (ALD).¹ As addiction specialists working in the area of liver transplantation in two other UK centres, we welcome his contribution to the debate, but take this opportunity to develop the argument

further and challenge some of his arguments and assumptions.

O'Grady offers us the opportunity to once again consider the issue of liver transplantation for ALD in a more articulate way by providing a useful overview of some of the pros and cons of transplanting this population, as well as carefully highlighting some of the dilemmas. Nevertheless, there are some facets of his report which need further exploration and indeed challenging.

Firstly, we accept that disease recurrence in the first 7-10 years after transplant is negligible when directly compared with the recurrence rates in viral hepatitis C virus (HCV), but it is misleading to prove the efficacy of transplantation for one medical indication by looking at outcomes in another. Historically transplant centres have measured outcome in terms of 5-year graft survival; however, in >40 years of liver transplantation, surgical, medical and drug management regimens have improved considerably and, therefore, it is not unreasonable to expect much greater graft survival in the ALD population. The HCV versus ALD debate is a limited one.

Secondly, we accept that historically too much emphasis has been placed on apparently arbitrary tests to determine candidate selection on ALD, and it would be useful to know which arbitrary tests O'Grady is referring to and how he defines these. In the UK, the liver advisory group (LAG) guidelines on transplantation for ALD² have at least offered transplant units a consistent and considered approach to candidate selection on the basis of current evidence. We would point out, however, that although the LAG guidelines do acknowledge the potential benefit of a period of abstinence, both for medical and alcohol stability and assessment, they do not actually advocate the 6-month rule as O'Grady suggests. We believe it is essential to make good use of the period of abstinence and take length of abstinence, and more importantly its context, into account. But assessment of likelihood of post-transplant abstinence incorporates so much more than this, such as acceptance of the diagnosis, degree of social support and meaningful occupation/replacement activities.³

O'Grady rightly points to some patients having ALD, but no diagnosis of alcohol dependence and vice versa, and anecdotally there is a notable ALD population transplanted with no dependence diagnosis. However, it is not uncommon for this cohort to resume alcohol use after transplant and often at levels that cannot be clinically ignored, whether or not their peers consume a similar amount.

Although it is true that repeated episodes of abstinence and relapse might sound alarm bells, the psychological framework of addiction medicine is rooted in patterns of lapse and relapse underpinned by the transtheoretical model of change.⁴ In other words, relapse is a natural part of the condition and although this needs to be carefully evaluated at an individual level in the context of organ shortage, and whether clear unambiguous medical advice has been received, it may well be that those who have experienced slips and relapses into drinking may emerge on the other side with greater insight and coping strategies. Therefore, it could be said that resumption of alcohol use after transplantation is not necessarily a failure from an addiction perspective, and if the graft is unharmed, then it is not a failure from a transplant perspective either. Clearly, this does not preclude abstinence as