Correspondence

Chronic hepatitis C in long term survivors of haematological malignancy treated at a single centre

In their review of 42 long term survivors of haematological malignancy Neilson *et al*¹ found two patients with hepatitis C virus (HCV) infection. Of the remaining eight patients with raised aspartate aminotransferase (AST) activity only two were explained by either hepatitis B virus infection or chronic graft versus host disease (GvHD), leaving six patients with unexplained liver dysfunction.

We are interested in the cause of continuing abnormal liver function in these patients in the light of our own experience of following long term survivors of haematological malignancy.

A review of our patients revealed that 21 were in complete remission more than three years after treatment. Two of these patients were HCV positive. They were diagnosed in 1986 and 1990 and received 41 and 28 units of blood, respectively. Five patients had raised AST activities, including both HCV positive patients. All five patients had serum ferritin concentrations (normal range 20-300 ng/ml) above the normal limit (median 863 ng/ml; range 395-4860 ng/ml). Three patients had hepatic siderosis confirmed on liver biopsy.

Murphy *et al*² reviewed survivors of allogeneic and autologous bone marrow transplant alive one year after transplantation and found that 38 (43%) of 88 had raised transferase activities not explained by either viral hepatitis or GvHD; 77% had a raised serum ferritin concentration consistent with iron overload and in 15/17 patients liver function improved after venesection.

Following treatment for haematological malignancy, transfusional iron overload is an important cause of increased transferase activity and should be considered when viral hepatitis and GvHD have been excluded. The long term outcome of untreated hepatic iron overload in this group of patients is uncertain but return of normal liver function after venesection suggests that this treatment may be beneficial. Maintenance of serum ferritin concentrations below 2000 ng/l has been shown to prevent complications in patients with iron overload.³ The role of venesection in patients with evidence of hepatic iron overload and normal liver function remains unclear.

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Drs Neilson and Harrison comment:

'We read Dr Butler's letter concerning the aetiology of the deranged liver function in our patients with great interest. We agree that iron overload may well be the cause of abnormal liver function in at least some of our patients and we have investigated this further. We have looked at both serum ferritin concentrations and non-transferrin bound iron in 38 of our patients, including the six with no obvious cause for liver dysfunction. Our initial results have been published in abstract form¹ and the full paper is published in this issue (see p853). We feel that it is worth emphasising that serum ferritin alone may not be a reliable indicator that iron overload is the cause of liver dysfunction. Hepatic damage itself leads to raised serum ferritin concentrations and like Murphy *et al*² we found that many patients without apparent liver dysfunction had very high serum ferritin concentrations. We agree that further study is required and we are currently involved in the MRC AML X iron overload study. This study aims to assess the effect of iron overload on liver function in surviving patients who were treated in the AML X trial. Several parameters of iron status, including serum ferritin and non-transferrin bound iron, will be assessed. Additional studies looking at putative markers for the haemochromatosis gene will be performed. We feel that this is an important area of research and would encourage others to respond favourably to requests for information and samples for the iron overload study.

- 1 Harrison P, Neilson JR, Marwah SS, Maddon L, Bareford D, Milligan DW. Iron overload, non-transferrin bound iron and liver dysfunction in long term survivors of haematological malignancy [abstract]. *Br J Haematol* 1996;93:25.
- 2 Murphy JA, Cook G, Mowat A, George K, Cameron S, McKenzie J, *et al*. Liver dysfunction in long term survivors of BMT due to hepatitis C virus (HCV) and transfusional iron overload: results of venesection therapy and liver biopsies. *Br J Haematol* 1995;89:5.

Bayesian Belief Network in histopathology

I read with interest the recent article by Montironi *et al* on the Bayesian Belief Network.¹ It is an important work because it gives general pathologists an overview of how subjective histological features in a grading system can be analysed mathematically. It is particularly impressive that a very precise probability matrix (normalised belief) can be reached at the conclusion of the mathematical analysis.

In spite of its apparent objectivity and precision, the Bayesian Belief Network depends very much on the conditional probability matrix (CPM) and the relative likelihood vector; the former is predetermined by experts and the latter by the observer. In the paper by Montironi *et al* the CPM constructed was based on the authors' experience. It is conceivable that different experts may have different CPMs and therefore different experts may arrive at totally different normalised beliefs even though they may agree on the same relative likelihood vector. With international consensus meetings, it may be feasible to standardise the CPM. However, it may be better still if the CPM is capable of renewing itself based on additional information from new cases.

Another source of interobserver inconsistency is the establishment of the relative likelihood vector, which carries with it an inherent

element of subjectivity. The idea of using video images stored on computer to minimise this inherent subjectivity is a very valid and thoughtful suggestion. It is theoretically possible to have a perfect match if the number of video images is sufficiently large.

As shown by boxes 1 and 2, Montironi *et al* suggested that the final belief probability matrix was determined by multiplying the three internal lambdas (from tubular formation, mitosis and nuclear pleomorphism). In order to justify multiplication as the best mathematical manipulation, it has to be assumed that the three parameters are independent variables. Recent studies,^{2,3} however, have shown that nuclear grade alone correlates with histological grade, suggesting that such an assumption may not be entirely correct. Therefore, I wonder whether it would be more reliable and accurate if the three internal lambdas are added together to get the final belief probability matrix. One may also take into consideration the relative importance of each parameter by first multiplying the individual internal lambdas by a scalar, followed by addition of the subsequent scaled internal lambdas. For example, if it is considered that tubular formation, mitosis and nuclear pleomorphism have a relative importance of 1:2:3 in the assessment of overall histological grade, the internal lambda for mitosis is multiplied by 2 and that for nuclear pleomorphism by 3 first and then added to the internal lambda for tubular formation to give the final belief probability matrix.

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- 1 Montironi R, Whimster WF, Collan Y, Hamilton PW, Thompson D, Bartels PH. How to develop and use a Bayesian Belief Network. *J Clin Pathol* 1996;49:194-201.
- 2 Hunt CM, Ellis EO, Elston CW, Locker A, Pearson D, Blamey RW. Cytological grading of breast carcinoma - a feasible proposition? *Cytopathology* 1990;1:287-95.
- 3 Cajulis RS, Hessel RG, Hwang S, Haines K, Frias-Hidvegi D, O'Gorman M. Simplified nuclear grading of fine-needle aspirates of breast carcinoma: concordance with corresponding histologic nuclear grading and flow cytometric data. *Diagn Cytopathol* 1994;11:124-30.

Standardisation of histopathology reports

I read with interest the paper concerning histopathology reports on primary cutaneous malignant melanoma.¹ It is surprising that even six years ago in approximately one in eight cases of malignant melanoma there was no comment on either tumour thickness or on completeness of excision of the tumour in the histopathology report. This is a good argument in favour of standardisation of reports particularly with respect to certain malignant tumours.

In the past pathologists have been reluctant to use standardised reports according to a predetermined protocol. However, the need for reports of this type is rapidly becoming more urgent.

Firstly, and most importantly, failure to mention important prognostic factors in a report on a particular type of tumour could be construed as negligent in a court of law. This is especially so in light of the fact that a standard textbook now contains prototype standardised reports for most important malignant tumours.² Secondly, pathologists should provide as much information in their

- 1 Neilson JR, Harrison P, Skidmore SJ, King HA, Collingham KE, Milligan DW. Chronic hepatitis C in long term survivors of haematological malignancy treated at a single centre. *J Clin Pathol* 1996;49:230-2.
- 2 Murphy JA, Cook G, Mowat A, George K, Cameron S, McKenzie J, *et al*. Liver dysfunction in long term survivors of BMT due to hepatitis C virus (HCV) and transfusional iron overload: results of venesection therapy and liver biopsies. *Br J Haematol* 1995;89:5.
- 3 Gabutti V, Piga A. Results of long-term iron-chelating therapy. *Acta Haematol* 1996;95:26-36.