Does Viral Hepatitis Cause Veno-Occlusive Disease in Patients with Renal Transplants?

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Dear Sir,

We read with interest the article written by Liano et al. [1] and would like to make the following points.

(1) We are totally in agreement with their conclusion that veno-occlusive disease, peliosis, hepatic sinusoidal fibrosis and nodular regenerative hyperplasia are interrelated. We have made similar observations [2] and postulated that the common histopathological denominator in these conditions is endothelial cell injury. We have shown in our cases which we followed sequentially by light and electron microscopy that there is transformation of endothelial cells as the disease progresses. In the sinusoids, the transformed endothelial cells in contrast to the normal have no cytoplasmic fenestrations, acquire basal lamina and Weibel Palade bodies, i.e. transformed from specialized into a non-specialized endothelial cell. The loss of cytoplasmic fenestration, acquisition of basal lamina and appearance of associated dense fibrosis in the Disse space may contribute to the portal hypertension on one hand, on the other hand this exerts a localized ischaemic effect on the adjacent hepatocytes with compensatory hyperplasia of others to produce nodular regenerative hyperplasia. In our series [2] we have postulated that azathioprine is the main aetiological agent but have not studied the details of the viral aspect of the patients and we submit that this should be looked at carefully in the future. As they suggested in their hypothesis is right, it will be interesting to compare liver biopsies from male patients with renal transplants and viral infections who are and are not under the cover of azathioprine.

(2) The definition of veno-occlusive disease of the liver used by the authors is a rigid one describing fibrous obliteration of the terminal hepatic vessels. We suggest that this is probably a late development in the disease. We suggest to include in such a definition the early (acute) phase reaction which is characterized by narrowing of the lumen by subendothelial oedema, fibrin deposition and loose connective tissue [3]. If we include that in the definition, then there is probably more in the literature than they have credited for [4].

It is possible to suggest that cessation of azathioprine in the acute «early» phase may lead to disappearance of veno-occlusive disease while if it is stopped later when the terminal venules are occluded by fibrosis, it will not reverse the condition of the venules.

The toxicity of azathioprine has been tested by Katzka et al. [5] and in one of our patients the lesion did not appear with subsequent biopsies after drug withdrawal. If veno-occlusive disease

is due to viral infection, it would be hard to explain the disappearance of the lesion with the cessation of the drug in the two cases.

The other point that needs considering in the observation that veno-occlusive disease in patients with renal transplant is much more commonly seen in male patients and for that they have no explanation. We would like to draw their attention to the literature which has shown similar findings regarding the whole spectrum. This includes veno-occlusive disease, peliosis, nodular regenerative hyperplasia and portal hypertension. We also have no explanation for this but the suggestion that there may be an idiosyncrasy of certain patients to develop this spectrum of disease is reasonable.

Finally, would the authors advise in such clinical situations as those illustrated in their article, to stop azathioprine?

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Response

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Dear Sir,

References

We would like to thank Haboubi et al. [1] for their comments on our paper on veno-occlusive hepatic disease in renal transplantation [2] published in *Nephron*.

Concerning the question about the treatment of these patients with azathioprine we think, as stated in the paper, that it seems reasonable, at the present level of knowledge, to stop azathioprine administration and to choose an alternative drug. Actually, we believe that ciclosporin seems the best alternative. No case of veno-occlusive hepatic disease has been observed in our last 130 kidney grafts treated with ciclosporin.

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