Lymphoproliferative processes and the liver

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The liver is rarely considered a lymphoid organ but nevertheless it is rich in immunocompetent cells. Normal portal tracts contain a mixture of CD3 and CD20 positive cells (predominantly the former), 15% of intrahepatic CD3 positive cells express the gamma delta receptor or which about one half co-express CD8. A further 30% of intrahepatic CD3 positive cells are thought to be natural killer T cells and co-excess CD56. There is a further population of CD3 positive cells that are CD4 and CD8 negative (null cells). In addition there are other cell types within the liver which can act as accessory cells. The Kupffer cells have at least a weak antigen presenting capacity but this has also been shown for sinusoidal endothelial cells and even hepatic stellate cells. In the right context, bile duct epithelium can also present antigen to immunocompetent cells and finally there are some true dendritic cells present principally within portal tracts.

Perhaps reflecting this lymphocyte-rich environment and the unique nature of the intrahepatic blood flow, the liver is a common site for lymphoproliferative disorders. Not unsurprisingly it is quite frequently involved in leukaemias. The pattern of infiltration in leukaemias varies according to the nature of the underlying myeloproliferative disorder. In both acute and chronic lymphocytic leukaemia, deposits are generally seen in portal tracts. In acute myeloid leukaemia infiltrates tend to be scattered throughout the liver, including portal tracts and parenchyma, while in chronic myeloid leukaemia there tends to be involvement of the sinusoids. Hairy cell leukaemia has a particular histological pattern with sinusoidal lymphocytosis often associated with peliosis and angiomatous lesions. Finally, large deposits may be seen within the liver parenchyma in multiple myeloma.

A number of groups have documented the pattern of involvement within the liver of systemic malignant lymphoma. Hepatic infiltration is most commonly seen in diffuse large B cell lymphomas but can also be observed in follicle centre cell lymphoma, marginal zone maltomas and in T cell neoplasms. Furthermore it has long been established that the liver can be involved in disseminated Hodgkin's disease. In broad terms the diffuse B cell neoplasms tend to show either large tumour nodules throughout the liver parenchyma or infiltrate portal tracts. A similar distribution is seen with follicle centre cell lymphomas but by contrast T cell lymphomas tend to show a sinusoidal pattern of infiltration. With many of these infiltrates there is relatively little impact on hepatic function. In some instances however the degree of infiltration is such that the patient may present with hepatic failure. When this is a manifestation of malignant lymphoma it may be indistinguishable from other causes of fulminant hepatic failure and early biopsy is mandatory.

Classical studies showed involvement of the liver in 55% of patients with Hodgkin's disease. This was based on autopsy studies but more recently biopsy studies have documented diagnostic lesions in less than 10% of cases. Involvement is most frequently seen with lymphocyte depleted and mixed cellularity types of Hodgkin's disease in which the infiltrates tend to form multiple small nodules. There are however other histological manifestations of Hodgkin's disease. Ductopenia for example is well described in Hodgkin's disease, the mechanism for this is uncertain but there are cases where this has reversed following treatment of Hodgkin's disease. Sinusoidal dilatation in the absence of obvious intrahepatic deposits is also described as is bilirubinostasis in the absence of obstructive lesions.

There are some lymphomas that can be regarded as "primary hepatic neoplasms". Maltomas resembling in many respects those seen in other internal organs such as the gastrointestinal tract are relatively uncommon. They are generally associated with some infiltration and destruction of bile ducts although true lymphoepithelial lesions may be indistinct. The cells within the infiltrate are CD20 and BCL2 positive but CD5 and CD10 negative. They are distinctive from other B cell hepatic neoplasms and run a more indolent course. A somewhat more common malignancy is the so-called T cell or histiocyte rich B cell lymphoma. This forms a subset of large B cell tumours and frequently patients with this neoplasm present with so-called B symptoms. On biopsy the malignancy is often either overlooked or misdiagnosed as Hodgkin's disease. This is in part due to there being a marked reactive T cell or CD68 response to the tumour cells and immunohistochemistry is generally required to pick out the malignant cells. The parenchymal reactive changes are almost certainly the result of cytokines released by the malignant cells. The tumour is

frequently seen within portal tracts and there may be an appearance of necrotising granulomas. The last group which are often considered within the spectrum of primary hepatic lymphoma are so-called hepatosplenic T cell neoplasms. These are essentially post thymic mature T cell malignancies and form a relatively small proportion of non-Hodgkin's lymphomas. The form which involves both the liver and spleen is generally one composed of small lymphocytes that express the gamma delta receptor. Occasionally some are of alpha/null receptor tumours. Irrespective of the receptor expression these malignancies have an aggressive course and some of the systemic effects are again likely to be due to the release of cytokines and chemokines. The gamma delta form is associated with a consistent presence of an isochromosome 7q.

Mention should be made of another intrahepatic "lymphoid neoplasm". The follicular dendritic cell tumour is characterised by an inflammatory psuedotumour-like appearance histologically but within the tumour there are CD21 and CD23 positive cells. These tumours frequently show a local infiltrative pattern but appear to have no, or certainly very low, metastatic potential. They are associated with EBV infection and several groups have now demonstrated an association with deletion in the latent membrane protein 1.

The above discussion is not meant to be exhaustive and there are other "miscellaneous" hepatic lymphomas. Occasional cases of intrahepatic plasmacytoma and angiocentric lymphoma have been identified and the liver can be involved in EBV driven lymphoproliferative diseases. In the simplest form it can be seen as part of a primary infection with the virus but in patients on immunosupression, a localised PTLD may be observed and can on occasions lead to significant liver dysfunction.