EDITORIAL

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Influence of Accompanying Chronic Hepatitis Status on Recurrence of Hepatocellular Carcinoma After Hepatectomy

Saiho Ko and colleagues,[1] in this journal, have focused on a most interesting feature of some hepatic carcinomas: that they can be not only multicentric but metachronous. These characteristics often become evident in the course of time as tumors of varying size appear in widely separated locations in the patient's liver, whether a resection of the originally recognized tumor has been performed in the meanwhile or not. In evaluating the nature of this process, one must consider how often the finding of multiple sites of malignancy can be attributed to the surreptitious spread of malignant cells as opposed to the repeated generation of new malignancies by a series of independent transformations. The latter possibility would require that widely separated cells change from a premalignant state into frankly malignant cells, yielding multiple tumors all with similar histologic characteristics. But it is just this kind of thing that appears to occur in the livers that these authors have studied, and they confirm that it occurs with a high frequency in certain groups of patients. It is a process that is accordingly of great importance to the patients concerned as well as being of considerable scientific interest.

The existence of "field changes" in certain tissues that mark them as under high risk for the repeated and continuing development of separate, new malignancies within the affected region is a phenomenon that has become more familiar in recent years. The stepwise genetic transformations that may lead to carcinoma of the colon, through intermediary stages in which benign polyps predominate, is one such situation, and certain patients with Barrett's esophageal transformation or with a demonstrably high propensity to have carcinomas of the skin develop seems to be another situation. Altered morphologic states in the liver itself, such as the presence of adenomatous hyperplasia, also have been identified clearly as premalignant.[2]

Here, the question of identifying premalignant states is directed toward liver tissue that is affected with various chronic inflammatory conditions. The authors of this article have studied 110 patients after liver resection for hepatocellular carcinomas in which the resection margins have been determined carefully to be negative. What, then, happened to the liver tissue remaining in place in terms of the development of further cancers? Were there any hints at the time of liver resection that can be used in classifying such patients regarding their risk of having new cancers? The possibility that further cancers could have been attributable to spread of the originally transformed cells is thought to have been pretty small, both because of the established negative resection margins and because new tumors were often multiple and widely distributed. This conclusion seems a reasonable one to me. It probably is supported also by what is known of the flow patterns of blood and lymph through the liver, which would not favor the likelihood of spread of malignant cells from one lobe to another.

In looking for information about premonitory factors for new malignancies, the authors have depended on their evaluation of the histologic status of the liver tissue remaining after hepatic resection. They are, of course, forced to make the assumption that the sample of liver available at the resection margin is representative of all the liver remaining behind, but this probably is fair enough because the changes in question are likely to be widespread and fairly uniform. In classifying the findings in their liver specimens, they used a rather antiquated system of categorizing the observed inflammatory changes[3] as newer systems have tended to subdivide the major classes that they used into multiple subgroups, mainly according to the severity of fibrotic changes as well as to the prevalence and location of inflammatory cells.[4] Using the categories they selected, the condition

that seemed the most ominous as a predictor of further malignant disease was chronic aggressive hepatitis. Chronic persistent hepatitis and cirrhosis were both associated less commonly with new hepatic malignancies, although the latter was more likely to be a harbinger of further malignancies than the former by a margin that was statistically significant. All these diagnoses are, of course, morphologic determinations of what is to be seen on sections of liver tissue rather than etiologic designations. All may represent various stages of viral hepatitis or may be attributable to quite different causes. The general designation of "liver cirrhosis" used by these authors exemplifies this, because cirrhosis can come about through numerous pathways and can even be a late stage of chronic persistent hepatitis. Viral hepatitis is one well-known precursor of hepatocellular carcinoma, especially where B virus is concerned. This relation appears to extend also to the more recently described C virus, but more information will be required to determine its full extent.[5] It is interesting that the tests of viral activity in the peripheral blood reported in the present paper uncovered no connection between the presence of circulating viral markers and the later development of new hepatic malignancies. Other tests of viral presence, including direct evaluation of viral substances in the liver, are, of course, possible and some, including *in situ* hybridization[6] and immunohistologic methods,[7] already have received attention.

The authors discuss their suspicion that the formation of new malignancies may be related to the amount of mitotic activity occurring in liver cells in association with chronic inflammation. This would fit well with the observation that chronic aggressive hepatitis is associated more closely with new cancers than chronic persistent hepatitis because one of the main differences between the two is the presence of damage to liver cells in the former, often with associated mitotic activity in response to cell destruction. They further suggest that the same fundamental mechanism may explain their observation that more new cancers appear to follow larger rather than smaller liver resections, the notion being that more mitotic activity will follow larger resections.

Primary liver cancer is less common in our Western environment than it is in some other parts of the world so that the search for a genetic background for the malignant transformations in question may be easier in places such as Japan, the origin of this article and of much recent information on the subject. One can suspect that some interesting genetic underpinnings will be discovered before long, the identification of which could be more helpful in individual cases than relying on histologic changes in the liver of a given patient to predict the future of that individual. Indeed, some appropriate efforts in this direction have been made already in animal systems,[8] and the involvement of the *p53* gene has undergone initial examination in human tumors, especially as an aid in determining whether multinodular tumors have arisen from a single precursor.[9]

To carry the subject further, it appears likely that new and better predictors than what are afforded by standard histologic examination will be required. This is because morphologic changes observable by conventional methods can have their cause in a variety of different initiating factors. For the present, this article points out the importance of continuing surveillance of patients who appear to fall into high-risk groups, because even present knowledge may be of some use, for example, in selecting patients for consideration of liver replacement at an earlier stage than might have seemed wise previously.

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