

Elsewhere Reviews

REGENERATING NODULES—ARE THEY PREMALIGNANT LESIONS?

Rapaccini GL, Pompili M, Caturelli E, Anti M, Aliotta A, Cedrone A, Amadei E, et al. Focal ultrasound lesions in liver cirrhosis diagnosed as regenerating nodules by fine-needle biopsy: follow-up of 12 cases. *Dig Dis Sci* 1990;35:422-427.

ABSTRACT

In the period 1985-1988, 62 focal liver lesions in 58 cirrhotic patients were studied by ultrasonography; 12 of these focal lesions were documented to be regenerating lesions by echo-guided fine-needle biopsy. During an average follow-up period of 10.2 months (range 3-22 months), hepatocellular carcinoma was subsequently found in 10 of the cases of regenerating nodules, whereas the initial diagnosis of regenerating nodule was confirmed in the remaining two cases. Based upon this finding, it is suggested that every focal mass visualized by ultrasonography in a cirrhotic liver should either be considered to be a neoplastic lesion or at least a preneoplastic lesion if the possibility of either a metastatic or benign lesion (eg hemangiomas, focal fatty liver change areas) can be excluded. Therefore either fine-needle aspiration or biopsy of all ultrasonographically revealed mass lesions within a cirrhotic liver is advised, such that early appropriate treatment for hepatocellular carcinoma can be instituted.

COMMENTS

This study attempts to address an important issue. What is the malignant potential of regenerative nodules in patients with cirrhosis? The authors identified 12 focal liver lesions that they termed "regenerative nodules" because they were histologically benign on initial evaluation. With mean follow-up of 10 mo, 10 of 12 (83%) of the regenerative nodules were demonstrated to be HCC. The authors discuss the two obvious options: (a) these were premalignant lesions that degenerated and became truly malignant; or (b) these were misdiagnosed initially and were malignant all the time.

It is essential to distinguish between regenerative nodules and focal lesions in a cirrhotic liver. Most patients with regeneration alone do not have focal lesions. Typically, regenerative nodules in patients with cirrhosis are recognized by irregularities of the liver

surface because they are isoechoic with the surrounding tissue and are not directly visible by ultrasound (1). If lesions are hypoechoic (as was the case for most of the lesions studied) or of mixed echogenicity, they are more likely to be malignant.

The authors identified 62 focal lesions from the ultrasonographs of 502 patients with histologically diagnosed cirrhosis. Less than 12.5% in this study had focal lesions, yet by definition all patients with cirrhosis have "fibrosis . . . with regenerative nodules" (2). The prevalence of malignancy in these focal lesions is very high because 89% were either initially or subsequently proven to be cancer. We are not given information about the prevalence of HCC in the other 87.5% of patients without focal lesions. This is important information, however, because if the prevalence in this group of patients was low, the overall incidence of 12.5% would be close to that expected in patients with cirrhosis. Thus ultrasound may simply be detecting those patients with HCC as evidenced by a focal lesion.

Inherent problems can be seen with all tests used in the evaluation of focal mass lesions. Tissue obtained by fine-needle aspirate (FNA) is not always adequate to distinguish well-differentiated HCC from benign hepatocytes. An ultrasound-guided liver biopsy procedure in which the hepatic architecture is preserved is more able to easily distinguish well-differentiated tumors from normal hepatocytes, but it is also subject to sampling error.

A recent study published in HEPATOLOGY (3) identified 160 nodular lesions by ultrasound and investigated them with a thin-needle biopsy procedure. The majority (82%) were malignant at initial evaluation. To rule out sampling error, benign lesions had biopsy procedures again within a few days. The 17 cases of benign regenerative nodules were observed for a year. No enlargement was demonstrated by ultrasound, and no lesion became malignant. Indeed, four of the lesions became undetectable by ultrasound. The authors concluded that large regenerative nodules are not premalignant lesions. Why do these apparently similar studies differ so radically in their conclusions? Possibilities include: (a) The initial evaluation to rule out malignancy was more rigorous in the second study. A biopsy rather than FNA was performed, and benign lesions were confirmed by repeat biopsy. (b) Considerable heterogeneity in the ultrasound patterns existed in the first study (which should raise the index of suspicion for malignancy), whereas all lesions in the second study were hypoechoic. (c) Most lesions in the second study were

undetectable by computed tomography (CT) scan. We are not given this information in the first study, but benign regenerative nodules are typically not visible by CT. If a focal lesion is confirmed by CT scan, again the question of malignancy should be raised. (d) Most lesions in the first study but not the second study enlarged with follow-up, which should also suggest HCC.

So what should we do with the asymptomatic patient with known cirrhosis and a focal lesion demonstrated by ultrasound? Most are going to have HCC. If the α -fetoprotein (AFP) level is high ($>1,000$ ng/ml), the patient almost certainly has HCC, and histological confirmation may not be necessary. A low AFP does not rule out malignancy. Although CT scan is not feasible for screening programs in the Far East, in the United States most ultrasound lesions will be confirmed by CT before obtaining the histological study. Ultrasound-guided, FNA should then be performed and, if histologically benign, repeated with a thin liver-biopsy needle. If the diagnosis of HCC is not made, the prudent course is to observe the patient. A rising AFP level and/or sonographic enlargement of the lesion should prompt further invasive evaluation by either an ultrasound-guided or laparoscopic biopsy procedure.

Are regenerative nodules premalignant lesions? The cirrhotic liver *per se* is associated with an increased risk of HCC, the risk varying with the cause of the liver disease. However, regenerative nodule is not synonymous with focal liver lesion. Every focal mass lesion in a cirrhotic liver should simply be considered malignant until proven otherwise (e.g., with a follow-up of more than 2 yr without observed progression). With careful evaluation, most will be shown to be malignant initially. The evidence that large regenerative nodules have greater malignant potential than the surrounding cirrhotic liver is slim at best.

TERESA L. WRIGHT
University of California, San Francisco
Gastroenterology Unit
VA Medical Center
San Francisco, California 94121

REFERENCES

1. Di Lelio A, Cestari C, Lomazzi A, Beretta L. Cirrhosis: diagnosis with sonographic study of the liver surface. *Radiology* 1989;172:389-392.
2. Lefkowitz JH. Pathologic diagnosis of liver disease. In Zakim, Boyer, eds. *Hepatology*. 2nd Ed. Philadelphia: W.B. Saunders Co., 1990.
3. Kondo F, Ebara M, Sugiura N, Wada K, Kita K, Hirooka N, Nagato Y, et al. Histological features and clinical course of large regenerative nodules: evaluation of their precancerous potential. *HEPATOLOGY* 1990;12:592-598.

LIVER TRANSPLANTATION RESTORES FEMALE REPRODUCTIVE ENDOCRINE FUNCTION

Cundy TF, O'Grady JG, Williams R. Recovery of menstruation and pregnancy after liver transplantation. *Gut* 1990;31:337-338.

ABSTRACT

The effect of successful liver transplantation on menstrual function was assessed by questionnaire in 44 women transplanted for various types of end stage liver disease, acute liver failure or malignant disease. Significant amenorrhoea ($>one$ year) was present in 48% of women with chronic liver disease before transplantation, and was reversed within 10 months of surgery in all but one of the pre-menopausal patients who had primary amenorrhoea and hypogonadotrophic hypogonadism. Two patients became pregnant five months and 1-5 years after transplantation, but in one instance the pregnancy was unsuccessful, possibly as a consequence of cyclosporin related intrauterine growth retardation.

Scantlebury V, Gordon R, Tzakis A, Koneru B, Bowman J, Mazzaferro V, Stevenson WC, et al. Childbearing after liver transplantation. *Transplantation* 1990;49:317-321.

ABSTRACT

Seventeen female patients who underwent orthotopic liver transplantation between June 1973 and June 1987 became pregnant 5 months to 11 years after transplantation. Immunosuppression was maintained with combinations of prednisone, cyclosporine, and azathioprine prior to and during pregnancy. One patient discontinued immunosuppression after knowledge of pregnancy, taking only azathioprine sporadically. Mean age at time of delivery was 26 years. Twelve patients had no alteration in liver function studies; 7 patients demonstrated mild or moderate enzyme elevations prior to delivery, with one case of rejection confirmed by percutaneous liver biopsy. Major problems related to pregnancy were hypertension, anemia, and hyperbilirubinemia. Twenty live births occurred (2 patients had 2 separate pregnancies, one patient has a set of twins); 13 were by caesarian section, 7 by vaginal delivery. Eleven of the 13 caesarian births were premature by gestational age. All vaginal births were term. Toxemia of pregnancy and early rupture of membranes were the principal indications for caesarean section.

There were no congenital abnormalities or birth defects and all the children are surviving well. Fifteen of 16 children older than one year have normal physical and mental development, with one child manifesting immature speech development. Four children are under one year, all with normal milestones thus far. Sixteen of the 17 mothers are alive from 2-18 years after transplantation; the only death was from a lymphoma, almost 4 years after transplantation and 2½ years after delivery. This experience suggests that women undergoing liver transplantation can safely bear children despite an increased risk of premature caesarian births. The effect of chronic immunosuppression of female pediatric patients on their reproductive potential later in adulthood remains to be fully evaluated but the results so far are favorable.

COMMENTS

In the past 20 yr, liver transplantation has emerged as the treatment of choice for many symptomatic patients