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Conversion of Micronodular Cirrhosis into Macronodular Cirrhosis

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The conversion from micro- to macronodular cirrhosis is claimed to be a general phenomenon. In this study, the conversion was quantitated by means of liver needle follow-up biopsies and autopsy in 156 patients followed in a controlled clinical trial of prednisone treatment in cirrhosis.

In the initial biopsy, 75 patients were classified as micronodular cirrhosis, and of them, 68 had macronodular cirrhosis at autopsy indicating a conversion ratio of about 0.9 in 10 years. This may overestimate the true conversion ratio slightly since conversion in many cases only was demonstrated at autopsy where the diagnosis of macronodular cirrhosis is made with greater certainty than from a needle biopsy. The median time interval between the diagnosis of micro- and macronodular cirrhosis was 2.25 years which is a maximum estimate of the conversion time due to irregular spacing between biopsies (or biopsy and autopsy). No significant difference was found between the conversion time in females and males. The conversion was faster in patients not drinking alcohol compared to patients drinking alcohol, but the difference was not significant. Prednisone treatment tended to accelerate the conversion, but not significantly.

Several attempts have been made to make a useful and reproducible morphological classification of cirrhosis (1, 2). At the moment, it is most usual to distinguish between regular and irregular cirrhosis, as suggested by Rubin and Popper (3), or between micro- and macronodular cirrhosis, as proposed by Sherlock (4) and Scheuer (5), and further recommended by WHO (6). The significance of this classification may be viewed in the light of its correlation to clinical, including etiologic, data, its reproducibility in biopsy and autopsy specimens, and its constancy. Concerning constancy, it is often assumed that one histological form may change into another during the course of the disease. Thus, Popper et al. in 1960 (7) described alcoholics with so-called "postnecrotic" (macronodular) cirrhosis, and nonalcoholics with so-called "portal" (micronodular) cirrhosis.

In 1962, Rubin et al. (8) published autopsy material comprising 342 liver specimens from patients with the diagnosis of "portal" or "postnecrotic" cirrhosis. Almost half of the patients with a clear history of alcoholism had "postnecrotic" cirrhosis. In addition, "postnecrotic features" were observed in many cases of "portal" cirrhosis with increasing frequency with the progression of the cirrhosis. These findings supported the hypothesis that "postnecrotic" cirrhosis in alcoholics might be the end-stage of "portal" cirrhosis. In addition, animal experiments have demonstrated transition from "portal" cirrhosis to "postnecrotic" cirrhosis in rats during recovery from a high-fat, low-protein diet (Hartcroft, W. S. and Grisham, J. W., *Fed. Proc.* 1960; 19:186, Abstract). Therefore, it is now generally accepted that micronodular cirrhosis may convert into macronodular cirrhosis, but this problem has not been analyzed in a sequential study.

The purpose of the present study was to evaluate from sequential observations the frequency and rate of this conversion and the possible influence of sex, alcohol consumption, and prednisone treatment on this process.

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MATERIALS AND METHODS

Between 1962 and 1969, a controlled clinical trial of prednisone treatment in 532 patients with cirrhosis was conducted by the Copenhagen Study Group for Liver Diseases (9). A liver biopsy was obtained by the Menghini technique at entry into the trial corresponding to the time of diagnosis. The patients were included if cirrhosis was demonstrated histologically acording to the criteria used at that time. Prednisone was given during the first months at a mean dose of 40 mg per day, gradually reduced to 10 to 15 mg per day as a maintenance dose. The patients were assessed regularly during the trial clinically, biochemically, and histologically until September, 1974. Further autopsy material available from patients who died after the study was terminated and before January, 1978 was collected. The median follow-up time for the total material was 27 months (range 1 to 148 months).

The original histological material included 532 initial biopsies, of which 488 were suitable for reclassification according to restrictive criteria (10). Biopsies from 287 patients fulfilled these criteria for cirrhosis, i.e., having at least two complete parenchymal nodules, and from 156 patients, autopsy specimens also showing cirrhosis were available (unpublished communication). Among these, 31 had follow-up biopsies (12 patients had 1, 12 had 2, 3 had 3, 2 had 4, and 2 patients had 7 biopsies; in total 67 follow-up biopsies), while the remaining 125 patients only had an initial biopsy and an autopsy specimen. The present material thus comprises 156 initial biopsies, 156 autopsy specimens, and 67 follow-up biopsies; in total 379 specimens.

Cirrhosis was classified as micronodular if the diameter of all nodules was equal to or less than 1.5 mm (the diameter of a normal lobule), and macronodular if the diameter of at least one nodule was more than 1.5 mm.

At the histological reclassification, several histological variables were evaluated, and among them the size of the parenchymal nodules as follows: (a) all parenchymal nodules were less than the size of normal lobules; (b) most of the biopsy consisted of nodules less than normal lobules, but nodules greater than normal lobules has been observed; (c) in about one-half of the biopsy, the nodules were larger than a normal lobule, and (d) most of the biopsy consisted of nodules larger than a normal lobule. Autopsy specimens containing only nodules larger than a normal lobule were included in Group D. In this study, Group A is classified as micronodular cirrhosis and Groups B, C, and D as macronodular cirrhosis.

Three observers (H. P., P. S. and L. F.) interpreted the biopsies independently on one occasion; if their evaluations differed, they reviewed the specimen together until all three agreed.

The length of the needle biopsies was graded as follows: (i) less than 5 mm; (ii) between 5 and 10 mm, and (iii) more than 10 mm. The degree of fragmentation was also graded semiquantitatively (0, +, and ++).

The life table method and the log-rank test (11) were used for temporal analysis of first occurrence of macronodular cirrhosis in patients with a micronodular cirrhosis at entry into the study. The "event time" is defined as the time from entry into the study to the first specimen showing a macronodular cirrhosis.

The effect of prednisone, sex, and alcohol was estimated using log-rank test (11). The relative occurrence was calculated as $(O_p/E_p)/(O_c/E_c)$, where O_p was the number of patients observed to show macronodular cirrhosis and E_p the number expected to show macronodular cirrhosis in the prednisone-treated group. O_c and E_c were the corresponding figures for the control patients.

RESULTS

Figure 1 shows the distribution of micro- and macronodular cirrhosis at entry (needle biopsy) and at autopsy. At the time of entry, there is an almost equal number of micro- and macronodular cases, i.e., 48 and 52%, respectively, while at autopsy the majority of the cases are macronodular (96%). Of the 75 cases with micronodular cirrhosis at entry, 68 had macronodular cirrhosis at autopsy. All of the 81 cases, initially classified as macronodular cirrhosis, had also macronodular cirrhosis at autopsy. It is seen from the figure that in the three subgroups of macronodular cirrhosis at autopsy, the distribution closely reflects that observed in the initial biopsy.

Figure 2 shows the conversion from micro- to macronodular cirrhosis in relation to time, i.e., the time interval from the initial biopsy showing micronodular cirrhosis to the first follow-up biopsy or autopsy showing macronodular cirrhosis. In half of the patients, the conversion has taken place before 2.25 years. Curve II includes only

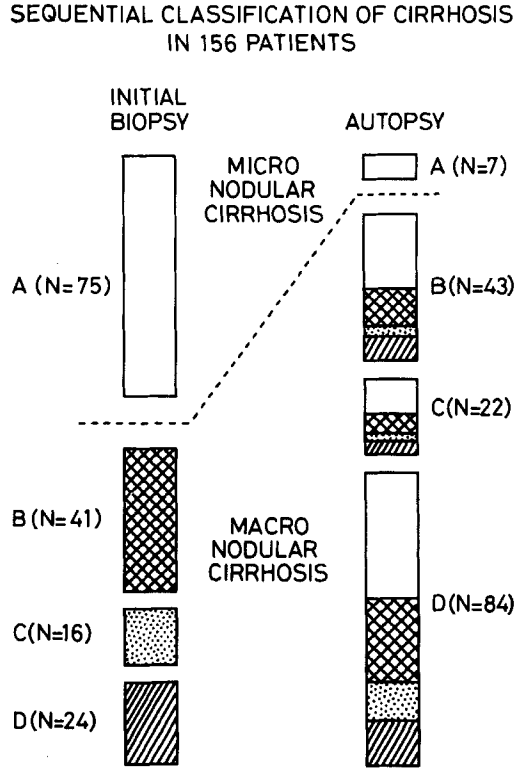

FIG. 1. Classification of cirrhosis according to size of parenchymal nodules in 156 patients at entry (corresponding to time of diagnosis) and autopsy. Signatures in column 2 refer to the original classifications in the initial biopsy (Groups A to D, see "Materials and Methods").

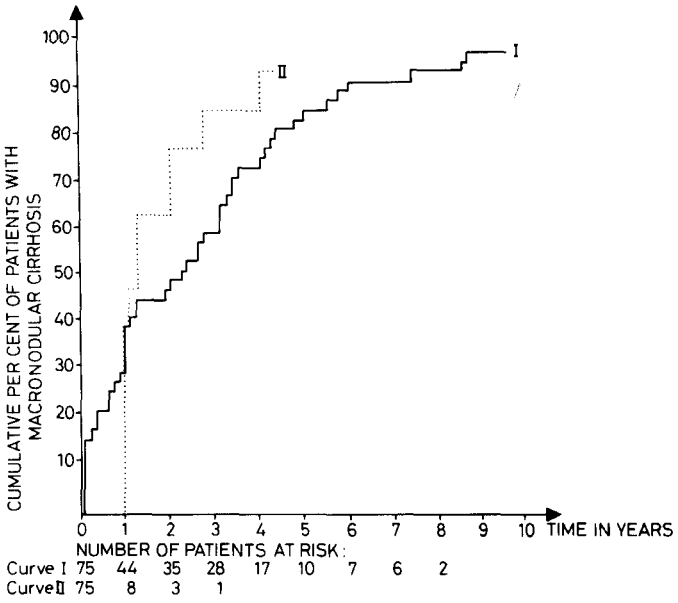

FIG. 2. Cumulative percentage of patients with macronodular cirrhosis developed from micronodular cirrhosis. *Curve I* (——), is based on the initial 75 biopsies with micronodular cirrhosis (Group A), the corresponding follow-up biopsies, and autopsy specimens. *Curve II* (· · ·) includes the initial biopsies and the available follow-up biopsies only.

the follow-up biopsies. The position of the curves is not significantly different.

The conversion time in females (= 23) and males (= 52) was not significantly different (p = 0.8), O/E female = 1.08 and O/E male = 0.97.

The conversion time in patients continuing drinking (= 40), patients stopping drinking (= 9), and patients never drinking alcohol (= 21) (five cases unknown) was not significantly different (p = 0.9). The O/E ++ alcohol = 1.02, O/E +− alcohol = 0.78, and O/E −− alcohol = 1.09.

In prednisone-treated patients (= 46), the median time of conversion was 1.3 years. In the control group (= 29 patients), it was 2.6 years. The O/E prednisone = 1.03 and O/E control = 0.96. This difference is not statistically significant (p = 0.89).

There were more small biopsies in patients with micronodular cirrhosis than in patients with macronodular cirrhosis (p = 0.005) (Table 1). The degree of biopsy fragmentation was not significantly different (p = 0.84).

DISCUSSION

The main purpose of the present study was to evaluate the frequency and rate of the presumed conversion of micronodular cirrhosis to macronodular cirrhosis. The present material comprised 75 cases classified as micronodular cirrhosis. This figure may be biased for the following reasons. First, the number depends on the applied definition of micronodular cirrhosis. We required all parenchymal nodules to be smaller than a normal lobule. Others (6) operate with a limiting diameter between micro- and macronodular cirrhosis of 3 mm. Our criteria were chosen because a needle biopsy with a limited diameter is unable to detect nodules with a diameter about 3 mm with reasonable certainty. Second, it cannot be excluded that large nodules might be found if larger tissue samples had been available, i.e., that the number of micronodular cirrhosis may be overestimated. The increasing frequency of micronodular cirrhosis with decreasing size of the biopsy (Table 1) may reflect this type of sampling error, but the alternative explanation, viz, that it is more difficult to get a large needle biopsy from a micronodular cirrhosis, is also likely.

For these reasons, the conversion frequency of 90% as found in the present material by comparing biopsy with autopsy specimens, should be regarded as a maximum value.

The estimated median time required for the development of macronodular cirrhosis from micronodular cirrhosis was found to be about 2 years. In order to evaluate the conversion time more precisely, follow-up biopsies would be required with short intervals. As this was not the case in the present material, the median conversion time found should be considered a maximum value. Since, however, the conversion frequency is also a maximum estimate, as stated above, these two possible errors will influence the conversion rate in opposite directions.

One should expect that the conversion from micronodular cirrhosis to macronodular cirrhosis took place successively from Group A over Groups B and C to Group D. For that reason, it is unexpected that the distribution of the three subgroups of macronodular cirrhosis at autopsy closely reflects that observed in the initial biopsy. Part of the explanation may be that the certainty of the diagnosis of macronodular cirrhosis on a needle biopsy is less than the diagnosis of micronodular cirrhosis even though in this case we also are biased by the sampling error.

Almost half of our material consisted at the time of entry of micronodular cirrhosis. This distribution is influenced by several factors such as the composition of the material as regards the etiology (i.e., early cases of alcoholic cirrhosis are micronodular, while many cases of posthepatitis cirrhosis are macronodular) and stage of disease. In addition, the applied definition of micronodular cirrhosis affects the result, for instance some use a diameter of the nodules of 3 mm and others 1 mm as the limit between micro- and macronodular cirrhosis. Finally, the distribution depends on whether the specimens are needle biopsies or autopsy material.

Females tended to convert faster than males, maybe because of a smaller percentage of alcoholics, but the difference was not significant.

TABLE 1. SIZE OF INITIAL BIOPSY IN PATIENTS WITH MICRONODULAR CIRRHOSIS (GROUP A) AND PATIENTS WITH MACRONODULAR CIRRHOSIS (GROUPS B + C + D)

Length of biopsy	Micronodular cirrhosis	Macronodular cirrhosis	Total
Smaller than 5 mm	10 (13%)	4 (5%)	14 (9%)
Between 5 and 10 mm	38 (51%)	23 (28%)	61 (39%)
More than 10 mm	25 (33%)	43 (53%)	68 (44%)
Surgical specimen	2 (3%)	11 (14%)	13 (8%)
Total	75 (100%)	81 (100%)	156 (100%)

The group which had never reported alcohol consumption tended to convert faster than patients with continued alcohol consumption, but insignificantly. As expected, the injury following alcohol consumption would probably inhibit the parenchymal regeneration.

Prednisone treatment tended to accelerate the conversion from micronodular cirrhosis to macronodular cirrhosis, but not significantly. The reduced activity, which prednisone treatment causes in some patients, may give rise to increased parenchymal regeneration and consequently larger parenchymal nodules.

In spite of the possible bias, we find that the results demonstrate that the conversion from micronodular cirrhosis to macronodular cirrhosis takes place in a considerable number of patients with cirrhosis, and it is likely that prednisone treatment accelerates this process.

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