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BREAST CANCER-ASSOCIATED ANTIGEN CA 15.3 IN LIVER CIRRHOSIS

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The tumor marker CA 15.3 was studied in 85 patients with liver cirrhosis. Nine patients (10.6%) had abnormal levels of CA 15.3 with the highest values in cases of Child's C patients. However, Child's classes were not significantly associated with the level of the antigen. We found significant correlations with some laboratory tests, especially IgA. All patients with an elevated CA 15.3 value also had abnormal levels of IgA, and multivariate analysis showed that IgA was the only independent factor associated with CA 15.3. Although IgA is a marker of alcoholic liver disease, other markers of alcoholism were not associated with CA 15.3. Cytolysis and cholestasis were not significantly associated with the CA 15.3 level, but liver dysfunction seemed to be involved. Liver disease does not substantially limit the usefulness of CA 15.3 in the cancer patient who also has liver cirrhosis, since both the percentage of abnormal values and the elevation of the serum levels are moderate in cirrhotic patients.

CA 15.3 is a glycoprotein that expresses two different epitopes which react with the monoclonal antibodies 115D8 and DF3 and whose radio-immunoassay was developed by Tobias et al. (1). 115D8 detects the MAM-6 antigen, present on most carcinomas, and certain normal epithelial cells, and was raised against human milkfat globule membranes (2). DF3 was prepared against a membrane-enriched fraction of human breast carcinoma (3). CA 15.3 is used mainly in the evaluation of breast cancer. There are increased levels in up to 60% of primary breast carcinomas and in up to 90% of the metastatic cancers, and the marker is also valuable for the follow-up of breast cancer patients (1, 4–10). Increased levels of CA 15.3 also occur in patients with cancer of liver, lung, ovary, endometrium and other organs (10–12).

A few studies have reported on the behavior of CA 15.3 in non-neoplastic liver diseases, with rates of elevated values ranging from 7% to 31% (9, 12–17). However, these studies have usually dealt with small numbers of patients with miscellaneous liver diseases, often poorly specified and mixed with other benign or malignant diseases. We have not found any studies specifically concerning the relationship between CA 15.3 and clinical or biochemical data in patients with liver cirrhosis. We have determined the serum levels of CA 15.3 in a large group of such patients, who were thoroughly evaluated form a clinical and laboratory viewpoint, to study the behavior of the antigen. We also searched for associations which might elucidate the mechanisms involved in the increase of CA 15.3.

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Material and Methods

The series included 85 patients with biopsy-proven liver cirrhosis, 65 males and 20 females, aged 25–83 years (mean 56.4 years). All patients were classified according to Child & Turcotte (18) with the modifications of Pugh et al. (19) and Christensen et al. (20), in Child A (n = 21), Child B (n = 32) and Child C (n = 32).

All patients were included in the study within 24 h of admission. Blood and urine were collected simultaneously for the laboratory determinations. The samples that were not processed immediately were frozen at −20°C until analysis. CA 15.3 was measured by immunoradiometric

assay (International CIS, France). The upper normal limit was established at 35 U/ml, corresponding to the mean +2 standard deviations of a control group of 275 healthy, HBsAg-negative individuals aged 16 to 66 years (mean 38.8 years).

Statistical analysis. For correlations between continuous variables the Spearman's rank-order correlation coefficient was used. The comparison between two categorical variables was made with the χ^2-test. The Kruskal-Wallis test and the Mann-Whitney U test were used to compare groups when appropriate. A p-value < 0.05 was used to denote statistical significance for a two-sided test. To assess the independent effect of predictor variables on the CA 15.3 level (dependent variable), a multivariate linear-regression modelling technique was used, with forward stepwise addition of variables, with a probability of < 0.05 for the F-test used as a criterion for the addition of a predictor variable.

Results

Only 9 patients (10.6%) had increased levels of CA 15.3. We found no differences in the CA 15.3 levels between the sexes, and age did not significantly influence the levels of the antigen. Table 1 depicts the CA 15.3 values according to the Child's classes. The highest levels were observed in Child's C patients. However, no statistically significant differences were found between Child's classes concerning the CA 15.3 level or the proportion of abnormal values. The correlation between CA 15.3 and other laboratory tests is shown in Table 2. The highest correlation coefficient found was with IgA.

No obvious relation was found between the CA 15.3 levels and etiology of the liver disease, portal hypertension, viral markers, smoking or alcoholic habits, quantity or duration of alcohol intake, previous treatment, consumption of drugs, malnutrition, previous gastrointestinal hemorrhages, icteric, ascitic or encephalopathic episodes, cholelithiasis, reason for admission, urinary bilirubin and urobilinogen, telangiectasis, spider naevi, hepatomegaly, splenomegaly or quantity of ascites.

We found no differences in the CA 15.3 levels between hyperbilirubinemic and normobilirubinemic patients, nor between patients with increased and normal values of ASAT. However, patients with abnormal levels of IgA had significantly higher CA 15.3 levels than those with a normal immunoglobulin value ($p = 0.007$). All 9 patients with an increased CA 15.3 level also had an increased IgA value, while none of the 14 patients with normal IgA had increased CA 15.3. Finally, at multivariate analysis using the standard liver tests, Child's grades and immunoglobulins, the only independent variable significantly associated with CA 15.3 was IgA.

Table 1

Values of CA 15.3 according to Child's classes

	Total	Increased	CA 15.3 values (U/ml)			
	n	n (%)	mean	SD	range	median
Child's A	21	2 (9.5)	21.5	9.5	8–42	20.0
Child's B	32	2 (6.3)	21.2	9.7	2–46	20.5
Child's C	33	5 (15.6)	24.1	13.4	3–60	23.5
All	85	9 (10.6)	22.3	11.1	2–60	21.0

SD: standard deviation

Table 2

Correlations between CA 15.3 and other laboratory parameters

Parameter	r	p
Hematocrit	−0.012	ns
Mean corpuscular volume	0.187	ns
Prothrombin activity (%)	0.003	ns
Partial thromboplastin time	0.008	ns
Fibrinogen	−0.133	ns
Aspartate aminotransferase (ASAT)	0.193	ns
Alanine aminotransferase (ALAT)	0.056	ns
Alkaline phosphatase	0.227	0.03
Gamma glutamyltranspeptidase (GGT)	0.083	ns
Lactic dehydrogenase (LDH)	0.220	0.04
Total bilirubin	0.187	ns
Direct bilirubin	0.140	ns
Cholesterol	0.049	ns
Glycocholic acid	0.243	0.02
Total protein	0.136	ns
Albumin	−0.047	ns
Gammaglobulin	0.285	0.006
IgG	0.230	0.03
IgA	0.356	0.0005
IgM	0.152	ns

r: Spearman's rank-order correlation coefficient
p: correlation coefficient's significance
ns: not significant

Discussion

CA 15.3 serum levels were slightly increased in a small proportion of our cirrhotic patients without malignancy. There are no reports that specifically investigate the behavior of this antigen in cirrhotic patients. Two papers dealing with miscellaneous benign or malignant diseases, report increased CA 15.3 in 6.7% of 30 patients with liver cirrhosis with a normal cut-off level of 30 U/ml (15), and in 27% of 26 cirrhotic patients with a cut-off level of 35 U/ml (14). These rates are similar to those reported for the antigen DF3 in 32 cirrhotics patients (19%) (21), although lower than the 80% reported for the antigen MAM-6 in 10 patients with liver cirrhosis (22).

The mechanism whereby the CA 15.3 concentration increases in these patients is unknown and, to the best of our knowledge, there is no reported study focusing on the metabolism of this antigen. As with other glycoproteins,

the metabolism of CA 15.3 can be impaired by liver dysfunction, as has been suggested for the antigen MAM-6 (22). Kudo et al. (23) observed reduced sialoglycoprotein receptor quantity related to progression of the liver disease, and Thomas & Zamcheck (24) reported that the liver plays an important role in clearance and excretion of glycoproteins. We have found a weak but significant correlation with glycocholic acid that is considered a marker of severity in liver diseases (25), and the highest values and percentages of abnormal levels were observed in Child's C cirrhotics. However, other clinical parameters and laboratory tests that reflect liver insufficiency were not associated with CA 15.3 and we have not found significant differences between the three Child's grades.

Without further clinical follow-up, our study is not adequate for evaluation of a possible prognostic value of CA 15.3. However, ascites, which has prognostic significance, was not associated with the CA 15.3 levels. We have not measured CA 15.3 in ascitic fluid. However, Kandylis et al. (26) did not find abnormal levels of the antigen in any of their patients with benign serous effusions, while increased values were frequently observed in serous effusions from patients with malignant diseases.

Neither cytolysis nor cholestasis, as measured by transaminases and bilirubin respectively, appeared to be related to the increase of the antigen in our patients. Of interest is the correlation that we have found with IgA. IgA is a reliable marker of alcoholic liver disease (27). However, CA 15.3 was not obviously associated with alcoholic etiology, alcoholic habits, daily alcohol intake, duration of alcohol intake, or other alcohol markers such as mean corpuscular volume and ASAT to ALAT ratio. However, the prevalence of abnormal IgA values in our patients was high (83.5%) and this finding needs further confirmation.

We conclude that cirrhotic liver disease is associated with moderately increased values of CA 15.3 in a small proportion of patients, and that a poor metabolism due to liver insufficiency can play a role in the increase of the antigen. Liver cirrhosis does not substantially limit the usefulness of this tumor marker in the cancer patient thanks to the fairly low rate of elevated values and the usually moderate elevation in cirrhotic patients.

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