Cancer Antigen 125 in Serum and Ascitic Fluid of Patients with Liver Diseases

Rafael Molina, Xavier Filella, Jordi Brux,1 Pedro Menguial, Jaume Bosch,1 Xavier Calvet,1 Judith Jo, and Antonio M. Ballestra

Serum concentrations of cancer antigen 125 (CA 125) were determined for 373 patients with various liver diseases: 57 with acute hepatitis, 57 with chronic hepatitis, 244 with liver cirrhosis (86 compensated and 158 decompensated), and 15 with primary liver cancer. The antigen was measured simultaneously in the serum and ascitic fluid of 46 of the patients with liver cirrhosis and sequentially in the serum and ascitic fluid of another 25 cirrhotics treated with paracentesis and (or) diuretics. Abnormal results for CA 125 were detected in sera from 4% of the patients with acute or chronic hepatitis, 60% of the patients with liver cirrhosis, and 67% of the patients with primary liver cancer. The main factor associated with abnormal serum concentrations of this antigen was the presence of ascites, with pathological CA 125 values in 94% of patients with ascites without jaundice (mean 566 ± 528 arb. units/mL), compared with only 40% of patients with jaundice and without ascites (mean 40.1 ± 28.5 arb. units/mL) (P <0.001). High concentrations of CA 125 were mainly associated with spontaneous bacterial peritonitis. The serum concentration of CA 125 decreased after treatment with paracentesis, but increased in patients treated with diuretics rather than paracentesis. The release of this antigen in liver cirrhosis appears to be independent of the liver disorder and, rather, results from peritoneal synthesis of this antigen.

Cancer antigen 125 (CA 125), a high-molecular-mass glycoprotein expressed in coelomic epithelium during embryonic development (1), is defined by a murine monoclonal antibody raised against a serous ovarian carcinoma cell line, OVCA 433. Kabawat et al. (2, 3), using immunohistochemical techniques, demonstrated the expression of CA 125 in the majority of ovarian epithelial tumors and its absence in most tumors of other etiologies. Subsequently, a radioimmunoassay to detect CA 125 in serum was developed by Bast et al. (4). Several studies have reported the clinical utility of this tumor marker in the follow-up of patients with ovarian adenocarcinomas (5–8).

CA 125 is not entirely specific for ovarian carcinoma. Above-normal concentrations have been measured in association with several benign and malignant diseases, including endometriosis and pelvic inflammatory diseases (9–15). We have previously reported similar increases of serum CA 125 in patients with ovarian cancer and in patients with decompensated liver cirrhosis (13, 16). Others have confirmed these results, but it is not clear how the abnormal concentrations of this marker are related to the liver pathology (12, 17–19).

The natural history of malignant ovarian carcinomas involves local invasion of tissues deep within the pelvis, frequently leading to peritoneal carcinomatosis and ascites. Ascites associated with liver cirrhosis is the main source of false-positive CA 125 results. The purpose of this study was to evaluate the mechanisms involved in the synthesis of CA 125 associated with benign liver disease and hence to speculate on the limitations of CA 125 as a tumor marker.

Materials and Methods

Concentrations of CA 125 in serum were evaluated in 57 patients with acute hepatitis, 24 with persistent chronic hepatitis, 33 with chronic active hepatitis, 244 with liver cirrhosis (86 compensated, and 158 decompensated), and 15 with primary liver cancer. Liver biopsy was performed in 199 of the patients with liver cirrhosis, which was cryptogenic in 51 cases, alcoholic in 86, positive for hepatitis B surface antigen in 17, and related to primary biliary cirrhosis in 45. The severity of the cirrhosis was assessed by taking into account the presence of ascites and the bilirubin concentrations, according to the cutoff values used in the classification of Child and Turcotte (20).

In 46 of the patients with decompensated liver cirrhosis, CA 125 was synchronously evaluated in ascitic fluid and in serum. CA 125 concentrations were also determined sequentially in serum and ascitic fluid in 25 of the patients with cirrhosis and ascites treated with paracentesis and (or) diuretics. Synchronous specimens of systemic and suprahepatic venous blood were taken from 25 patients with liver cirrhosis.

CA 125 concentrations were determined in duplicate by a commercial immunoradiometric procedure (Sorin Biomedica, Milan, Italy). Normal values were defined as concentrations <35 arb. units/mL. In addition, bilirubin was determined in 199 of the patients with liver cirrhosis (135 decompensated and 64 compensated) with use of a Prisma multichannel autoanalyzer (Clinicon, Malmo, Sweden), 22.3 μmol/L being considered the upper normal limit. Statistical analyses were done by the Kolmogorov and chi-square tests for qualitative results and by the Mann–Whitney U-test for quantitative results.

Results

Table 1 summarizes the CA 125 concentrations in patients with various types of liver diseases. Only 4.4% (five of 114) of patients with acute or chronic hepatitis showed above-normal values for the tumor marker; the
mean CA 125 value for the group was within the normal range. In contrast, CA 125 concentrations >35 arb. units/mL were found in 60% of patients with liver cirrhosis and in 66.6% of patients with primary liver cancer. There were no significant differences between the CA 125 concentrations found in these two groups of patients; however, the concentrations were significantly higher in the cirrhotic and cancer patients than in the patients with acute or chronic hepatitis without cirrhosis (P <0.0001).

The patients with uncompensated cirrhosis presented higher CA 125 concentrations than did compensated patients with cirrhosis (Table 1) (P <0.0001). The latter group had CA 125 serum concentrations similar to those found in the patients with acute or chronic hepatitis.

The possible relationship between CA 125 serum concentrations and the etiology of the liver cirrhosis is explored in Table 2. We saw no obvious relationship between the physiopathology of liver cirrhosis and the serum concentrations of this tumor marker. The highest values for CA 125 were found in uncompensated cirrhotics, independent of etiology.

Table 3 shows the relationship between the CA 125 serum concentrations and the type of decompensation in liver cirrhosis. The concentrations of this antigen in patients with uncompensated cirrhosis (excluding the cases of primary biliary cirrhosis) did not change in relation to the bilirubin concentration, the mean CA 125 being 529 (SD 553) arb. units/mL in subjects with bilirubin concentrations <34.2 μmol/L and 540 (SD 621) arb. units/mL in subjects with bilirubin >60 μmol/L. In patients with compensated primary biliary cirrhosis, CA 125 serum concentrations (mean 18.6, SD 11.7, arb. units/mL) were similar to those found in other types of cirrhosis and were independent of bilirubin concentrations (Table 3). CA 125 concentrations in patients with uncompensated primary biliary cirrhosis, 219.0 (SD 258) arb. units/mL, were no different from those in other types of cirrhosis, despite the higher bilirubin concentrations (mean 230, SD 171, μmol/L).

Table 4 shows the CA 125 serum concentrations in patients with compensated cirrhosis in relation to the presence of ascites and the concentration of bilirubin. The majority of patients with ascites (86 of 96) again presented with above-normal CA 125 concentrations, independent of the bilirubin concentrations. Of the patients with jaundice (bilirubin >60 μmol/L) but without ascites, 40% also had above-normal CA 125 concentrations, although lower than those found in patients with ascites (P <0.0001).

Figure 1 shows the CA 125 concentrations found in ascitic fluid and in serum from the patients with uncompensated liver cirrhosis in relation to the presence or absence of infection in the ascitic fluid. In both serum and ascites, the concentration of CA 125 was very high. In patients with spontaneous bacterial peritonitis, CA

### Table 1. Serum Concentrations of CA 125 in Patients with Liver Diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>No. (% total) (and %)</th>
<th>Mean</th>
<th>Median</th>
<th>SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Conc. arb. units/mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute hepatitis</td>
<td>3/57 (5)</td>
<td>19.3</td>
<td>6.0</td>
<td>41.0</td>
<td>6–263</td>
</tr>
<tr>
<td>Chronic persistent hepatitis</td>
<td>1/24 (4)</td>
<td>17.3</td>
<td>17.0</td>
<td>20.3</td>
<td>6–109</td>
</tr>
<tr>
<td>Chronic active hepatitis</td>
<td>1/33 (3)</td>
<td>18.0</td>
<td>7.5</td>
<td>22.0</td>
<td>6–126</td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td>147/244 (60)</td>
<td>381.0</td>
<td>126.0</td>
<td>640.0</td>
<td>6–4484</td>
</tr>
<tr>
<td>Compensated</td>
<td>8/36 (9)</td>
<td>33.3</td>
<td>10.0</td>
<td>88.4</td>
<td>6–284</td>
</tr>
<tr>
<td>Decompensated</td>
<td>139/158 (88)</td>
<td>582.8</td>
<td>388.0</td>
<td>730.0</td>
<td>6–4464b</td>
</tr>
<tr>
<td>Primary liver cancer</td>
<td>10/15 (67)</td>
<td>378.0</td>
<td>104.0</td>
<td>573.0</td>
<td>6–1740b</td>
</tr>
</tbody>
</table>

* With values exceeding 35 arb. units/mL.
* Significantly different from uncompensated liver cirrhosis: P <0.0001.
* Significantly different from uncompensated liver cirrhosis: P <0.05.

### Table 2. Serum Concentrations of CA 125 In Patients with Liver Cirrhosis, According to the Etiology of Cirrhosis and Presence (D) or Absence (C) or Decompensation

<table>
<thead>
<tr>
<th>Etiology</th>
<th>No. (% total and %)</th>
<th>Mean</th>
<th>Median</th>
<th>Conc. arb. units/mL</th>
<th>SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryptogenic C</td>
<td>2/26 (8)</td>
<td>18.0</td>
<td>11.5</td>
<td>18</td>
<td>6–81</td>
<td>6–4464b</td>
</tr>
<tr>
<td>D</td>
<td>59/70 (84)</td>
<td>602.9</td>
<td>374.0</td>
<td>844</td>
<td>6–395</td>
<td>6–300b</td>
</tr>
<tr>
<td>Alcoholic C</td>
<td>4/18 (22)</td>
<td>52.4</td>
<td>8.2</td>
<td>103</td>
<td>6–4464b</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>64/68 (94)</td>
<td>651.0</td>
<td>456.0</td>
<td>689</td>
<td>6–300b</td>
<td>6–700b</td>
</tr>
<tr>
<td>HbAg + C</td>
<td>2/10 (20)</td>
<td>35.6</td>
<td>8.0</td>
<td>49</td>
<td>6–300</td>
<td>23–918b</td>
</tr>
<tr>
<td>D</td>
<td>7/7 (100)</td>
<td>327.0</td>
<td>350.0</td>
<td>203</td>
<td>6–35</td>
<td>23–918b</td>
</tr>
<tr>
<td>PBC C</td>
<td>0/32 (0)</td>
<td>18.6</td>
<td>10.0</td>
<td>117</td>
<td>6–35</td>
<td>23–918b</td>
</tr>
<tr>
<td>D</td>
<td>9/13 (69)</td>
<td>249.0</td>
<td>149.0</td>
<td>258</td>
<td>6–35</td>
<td>23–918b</td>
</tr>
</tbody>
</table>

* With values exceeding 35 arb. units/mL.
* Significantly different from value in uncompensated liver cirrhosis: P <0.0001.

PBC: primary biliary cirrhosis.
Table 3. Relation of Bilirubin Concentrations to Serum Concentrations of CA 125 in Patients with Decompensated Liver Cirrhosis

<table>
<thead>
<tr>
<th>Bilirubin concn, µmol/L</th>
<th>No. % total (and %)</th>
<th>Mean</th>
<th>Median</th>
<th>SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excluding cases with primary biliary cirrhosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;34.2</td>
<td>34/40 (85)</td>
<td>529.0</td>
<td>352.0</td>
<td>553</td>
<td>35-2055</td>
</tr>
<tr>
<td>34.2-60</td>
<td>24/26 (92)</td>
<td>427.0</td>
<td>250.0</td>
<td>289</td>
<td>14-2000</td>
</tr>
<tr>
<td>&gt;60</td>
<td>40/56 (87)</td>
<td>540.0</td>
<td>273.0</td>
<td>521</td>
<td>7-2294</td>
</tr>
<tr>
<td>Cases with primary biliary cirrhosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>68.4-169</td>
<td>0/32 (0)</td>
<td>18.6</td>
<td>10.0</td>
<td>11.7</td>
<td>6-35(^b)</td>
</tr>
<tr>
<td>169</td>
<td>9/13 (69)</td>
<td>219.0</td>
<td>149.0</td>
<td>258</td>
<td>23-918(^b)</td>
</tr>
</tbody>
</table>

\(^a\) With values exceeding 35 arb. units/mL.
\(^b\) Significantly different from each other: P <0.0001.

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Table 4. Effect of Jaundice or Ascites on Serum Concentrations of CA 125 in Patients with Decompensated Liver Cirrhosis

<table>
<thead>
<tr>
<th></th>
<th>No. % total (and %)</th>
<th>Mean</th>
<th>Median</th>
<th>SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jaundice without ascites(^a)</td>
<td>8/20 (40)</td>
<td>40.1</td>
<td>34.0</td>
<td>28.5</td>
<td>7-100</td>
</tr>
<tr>
<td>Jaundice with ascites(^c)</td>
<td>28/30 (94)</td>
<td>533.0</td>
<td>470.5</td>
<td>475</td>
<td>7-2294(^d)</td>
</tr>
<tr>
<td>Ascites without jaundice</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ascites bilirubin &lt;34.2 µmol/L</td>
<td>32/34 (94)</td>
<td>566.0</td>
<td>352.0</td>
<td>528</td>
<td>35-2055</td>
</tr>
<tr>
<td>Ascites bilirubin 34.2-60 µmol/L</td>
<td>28/32 (81)</td>
<td>441.9</td>
<td>227.5</td>
<td>505</td>
<td>14-2000</td>
</tr>
<tr>
<td>No jaundice, no ascites</td>
<td>2/6 (33)</td>
<td>38.5</td>
<td>29.5</td>
<td>24.7</td>
<td>14-75</td>
</tr>
</tbody>
</table>

\(^a\) Excluding patients with primary biliary cirrhosis.
\(^b\) With values exceeding 35 arb. units/mL.
\(^c\) Bilirubin >60 µmol/L.
\(^d\) Significantly different from patients with jaundice but without ascites: P <0.0001.

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Fig. 1. CA 125 concentrations in serum and ascitic fluid from patients with liver cirrhosis, subdivided according to the presence or absence of spontaneous bacterial peritonitis

125 was significantly higher than in the cases without infection (P <0.001). Results in serum were similar but not statistically significant. In patients with ascitic infection, the highest concentrations of CA 125 were found in ascitic fluid rather than in serum.

Nineteen of 25 patients with serial CA 125 serum determinations during treatment showed a decrease in this antigen in serum during follow-up. Of those treated with paracentesis, 90% (18 of 20) showed a significant decrease of CA 125 (Figure 2). One of only two patients showing an increase of the tumor marker had primary liver cancer. In contrast, only one of the six patients receiving diuretic treatment showed a decrease in antigen concentration (Figure 3). The CA 125 concentrations in the ascitic fluid of most of the patients were lower than in serum.

The serum concentrations of CA 125 from peripheral

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Fig. 2. Sequential CA 125 determinations in patients with liver cirrhosis with ascites treated with paracentesis (▼)
Numbers above the lines are the CA 125 concentrations (arb. units/mL) in ascitic fluid

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veins (mean 245 ± 308 arb. units/mL) and from suprahepatic veins (272.2 ± 371 arb. units/mL) showed no significant differences. Again, the patients with ascites presented higher concentrations of the marker. The mean concentrations of CA 125 in the cases without ascites were similar in both veins (31.1 ± 21.5 vs 31.6 ± 22.5 arb. units/mL). In the cases with ascites, the concentration was higher in blood from the suprahepatic vein (407 ± 407 arb. units/mL) than in peripheral blood (364 ± 330 arb. units/mL), although the differences were not significant.

Discussion

Several studies have indicated the utility of CA 125 in follow-up of patients with ovarian carcinoma (4-8). Like many other tumor markers, CA 125 is not a tissue- or tumor-specific antigen; thus, above-normal concentrations of it are found in serum in several benign and neoplastic pathologies (4, 5, 9-15). The majority of false-positive results arise in association with liver diseases, particularly cirrhosis (12, 13, 16-18).

Liver diseases without malignant transformation are frequently associated with increases of various tumor markers in serum, including alpha-fetoprotein, carcinoembryonic antigen, and cancer antigen 19.9 (CA 19.9) (21-24). The causes for the association of tumor markers with liver diseases vary. For example, increases in serum alpha-fetoprotein arise in association with liver regeneration (21, 25), whereas disorders in catabolism and excretion are often associated with increases in carcinoembryonic antigen or CA 19.9 (22-24). Our observation of above-normal CA 125 in patients with liver diseases argues against cytolysis as the cause for the increase of CA 125 detected in liver diseases. The incidence of above-normal CA 125 in hepatitis, independent of etiology, was 4.4%, with mean values being the normal range. These results are similar to those described by our group in previous studies and by others (12, 13, 16-18).

The highest concentrations of CA 125 in liver diseases are seen in cirrhotic patients. Ruibal et al. (12) suggested that cholestatic disorders such as cirrhosis, liver cancer, and liver metastasis are the cause of increases in CA 125. Eerdekens et al. (19) reported a relationship between jaundice and increased concentrations of CA 125. In our experience, the serum concentrations of this marker are independent of the etiology of the cirrhosis, whereas in all types of cirrhosis, increased CA 125 is observed, mainly among patients with decompensated liver disease.

The presence of ascites and the bilirubin concentration are the variables most frequently used to assess the existence of liver decompensation (20). Bilirubin does not seem to be related to increases in CA 125 concentrations. Furthermore, the CA 125 concentrations in patients with primary biliary cirrhosis, a highly cholestatic chronic liver disease, were similar to those seen in cirrhosis of other etiologies—results that contradict those reported by Eerdekens et al. (19).

In contrast, the presence of ascites seems to play a key role in the mechanism responsible for increased CA 125. The mean concentration of CA 125 is much higher in cirrhotic patients with ascites than in patients without ascites and also is higher than in jaundiced patients (P < 0.0001). These results are similar to those previously reported by our group (16) and by Bergman et al. (18). The causal relationship between an increase in CA 125 and ascites is further suggested by the high concentrations of the antigen in ascitic fluid, especially in cases diagnosed with bacterial peritonitis. Our results suggest that a possible source of this increase in CA 125 is nonspecific stimulation of CA 125 synthesis by the pleural and peritoneal mesothelium, which contain CA 125 (3). An increase in the release of CA 125 by cell lysis in infection may also play a role in the increases in serum and ascitic CA 125.

The relationship between serum and ascitic concentrations of CA 125 varies considerably. In cases with infection in the ascitic fluid, concentrations are usually higher in ascites than in serum. The opposite is true in the absence of infection, with major individual variations. The idea of a serum–ascitic fluid exchange is supported by the decrease in serum CA 125 observed in patients with ascites who are undergoing therapeutic paracentesis (with ≥4 L of fluid). These patients show a considerable decrease in serum CA 125 concentrations within a few days. This decrease in serum CA 125 does not occur in patients treated with diuretics. In fact, most of the latter patients show an increase in the serum concentrations of CA 125. Paracentesis decreases the volume of ascitic fluid, which has a high concentration of CA 125, and thereby causes an absolute decrease in the amount of this antigen in the abdominal cavity. If CA 125 passes from ascitic fluid to the serum, this could explain the subsequent decrease in the serum concentrations of CA 125 in patients treated by paracentesis. Diuretic treatment involves the passage of fluid from ascites to serum, followed by renal excretion. The increase in the serum concentrations of CA 125 in patients treated with diuretics may thus be caused by the passive
passage of this antigen from the abdominal cavity to the serum.

The absence of increases in CA 125 in cytolytic liver disease and the fact that concentrations of CA 125 are similar in peripheral and suprahepatic blood, together with the slight influence of jaundice on serum concentrations of CA 125, strongly argue against the idea that the liver is the direct source (by synthesis or by release in cytolysis) or indirect source (e.g., in metabolic disorders) of CA 125 increase. The presence of CA 125 in mesothelial, the high concentration of CA 125 found in ascitic fluid, the increase of CA 125 in association with infections of the ascitic fluid, and the decrease detected in serum CA 125 after paracentesis suggest that the ascitic fluid is a reservoir for the antigen, which is synthesized by the peritoneum. These results are provoking because CA 125 is a high-molecular-mass glycoprotein, which might be expected to pass from ascites to serum only with difficulty.

One of the primary clinical applications of measuring serum CA 125 is to monitor disease progression in patients with ovarian carcinoma, a type of cancer often associated with ascites. Our results suggest that increases in CA 125 in this situation may be at least partly the result of peritoneal rather than tumor synthesis. This idea is consistent with the observation that, although CA 125 is rarely detected in mucinous carcinomas by immunohistochemistry (2, 26, 27), increased concentrations of CA 125 in serum have been reported in 60% of such patients with advanced disease and ascites (28, 29).

In conclusion, our results suggest that the main cause for the increase of serum CA 125 in various benign liver diseases is the presence of cirrhosis and ascites. This antigen may be synthesized in the pleural mesothelium and released into the ascitic fluid or serum. The ascitic fluid may act as a reservoir for the antigen, which then passes into the circulation.

We thank Celia Aparicio and Francisca Coca for their technical assistance.

References