Placental Alkaline Phosphatase and Cancer Antigen 125 in Sera of Patients with Benign and Malignant Diseases

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Human placental alkaline phosphatase (hPLAP; EC 3.1.3.1), cancer antigen 125 (CA 125), and carcinoembryonic antigen (CEA) were determined in sera of patients with malignant and nonmalignant disorders. For CA 125 we used two different commercial assay systems, based on the same monoclonal antibody. hPLAP had the same sensitivity (20%) as CA 125 for detecting non-ovarian neoplasia, whereas that of CEA was 45%. For detecting ovarian cancer CA 125 (Cis kit) was slightly more sensitive (50%) than hPLAP (45%), much more than CEA (10%). hPLAP was increased in sera of 2% of patients with nonmalignant disorders, CA 125 in 23%, and CEA in 18%. hPLAP was increased in only one of 10 diabetic patients and two of 50 patients on chronic renal dialysis. CA 125 and CEA were respectively increased in 45% and 23% of all liver pathologies studied and in 12% and 17% of patients with renal insufficiency. The sensitivity of hPLAP for detecting ovarian cancer is slightly inferior to that of CA 125, but its specificity is much higher. We found the Abbott system for CA 125 to be more sensitive than the Cis system.

Additional Keyphrases: carcinoembryonic antigen · ovarian cancer · renal dialysis · liver disease · diabetes · cutoff value · receiver operating characteristic curves · "kit" methods

Late diagnosis is one of the major factors contributing to the poor prognosis of ovarian cancer, placing this disease near the top in the mortality statistics for all gynecological malignancies (1). Earlier recognition by specific measurement of tumor markers in the circulation might enhance therapeutic success.

Bast et al. (3) recently introduced a cancer antigen 125 (CA 125) that is considered promising for the follow-up of ovarian epithelial cancer (2). Human placental alkaline phosphatase (hPLAP; EC 3.1.3.1), known as a tumor marker since 1968 (3), has gained new interest as a tumor marker now that highly specific monoclonal antibodies have become available (4, 5). Therefore we have compared the specificity and the sensitivity of hPLAP and CA 125 in patients with ovarian and nonovarian cancers and in patients having a selected series of benign chronic disorders. We determined hPLAP as previously described (4) with an assay system that is highly specific and sensitive (4, 6). A serious disadvantage of CA 125 is that the concentrations of this marker in serum reportedly are increased in several benign disorders (7). We determined CA 125 with two assay systems, each based on the same monoclonal antibody (OC 125). We also determined CEA, given its widespread use in clinical practice as a general tumor marker.

Materials and Methods

We studied 20 patients with ovarian cancer, as well as patients with nonovarian cancers (13 gastric, 15 colorectal, three mammary, two renal, one prostatic, five pancreatic tumors, one tumor of unknown origin, three with leukemia, and two with lymphoma), and patients with chronic nonneoplastic diseases (10 diabetics, 19 with renal insufficiency, 50 receiving chronic dialysis, 24 icteric noncirrhotic, nine icteric cirrhotic, and 14 cirrhotic nonicteric patients). The group of benign chronic disorders included no patients with a concomitant malignancy.

Fresh serum samples from those subjects were frozen and stored in liquid nitrogen. The samples were thawed only once, just before analysis. No hemolytic samples were included, because interference by hemolysis with determination of CA 125 is mentioned by the manufacturers.

Ovarian cancer patients were staged according to the classification guidelines of the International Federation of Gynecology and Obstetrics.

We determined hPLAP with a specific enzyme antigen immunoassay based on a mouse monoclonal antibody to hPLAP (<0.02 U/L), but were measured for CA 125 [25 ± 5] kU/L, and for CEA [2.5 ± 0.6] μg/L.

CEA concentrations were increased in 45% of the patients with nonovarian tumors, whereas hPLAP and Cis CA 125 the CA 125 RIA kit from Abbott Diagnostic Division, North Chicago, IL, which involves the same monoclonal antibody. Serum CEA concentrations were determined by radioimunoassay (polyclonal CEA-RIA kit, Abbott). We used all commercial kits according to the manufacturers' instructions. We used a spline-function program to calculate the standard curves from which we determined the antigen concentration in samples.

Results

Table 1 summarizes the results for hPLAP, Cis CA 125, and CEA in the different groups studied. We used cutoff values of 0.1 U/L for hPLAP (4), 35 and 65 kU/L for CA 125 (2), and 5.4 μg/L for CEA. Mean (± SD) results for five healthy blood donors were below the detection limit for hPLAP (<0.02 U/L), but were measured for CA 125 [25 ± 5] kU/L, and for CEA [2.5 ± 0.6] μg/L.

CEA concentrations were increased in 45% of the patients with non-ovarian tumors, whereas hPLAP and Cis CA 125 were each increased in 20% of these patients. hPLAP activities >0.2 U/L, the lowest activity always associated with neoplasia in an average hospital population (4), were observed in one patient with gastric carcinoma, one with colon tumor, one with a pancreatic carcinoma, and one with carcinoma of the breast. In the last three of these patients CEA and Cis CA 125 were also increased.

Of the patients with ovarian cancers, 10% had an increased concentration of CEA, in contrast to hPLAP and CA 125, which were increased in 45% and 50% of these patients, respectively. Of the nine ovarian cancer patients with
increased activities of hPLAP in their sera, four were in stage I, three in stage III, and two in stage IV. Eight of 10 of those with increased values for Cis CA 125 were in stage III or IV. Of those with increased CA 125 as measured with the Abbott assay system, three were in stage I, one in stage II, three in stage III, and four in stage IV.

Well-defined groups of benign chronic diseases were studied. In the group of diabetic patients, only a heavy smoker showed increased values for hPLAP (0.15 U/L), and he showed no increased values for Cis CA 125 or CEA.

None of the patients with mild renal insufficiency and 4% of those with severe renal insufficiency had increased hPLAP activity. However, for mild as well as for severe renal insufficiency the percentage increases were, respectively, 8% to 21% for CA 125 and 11% to 20% for CEA.

The group of patients with liver diseases showed no increase in hPLAP (Table 1). In contrast, concentrations of Cis CA 125 in serum of patients with hepatic disease were increased by more than 35 U/mL in eight of the nine (88%) icteric cirrhotic patients, and in 29% and 43% of the icteric noncirrhotic and cirrhotic patients, respectively. If we used 65 kU/L as an arbitrary cutoff value for CA 125, as did Bast et al. (2), 78% of the patients with cirrhosis still had increased activities of this marker. The results for Cis CA 125 in sera of patients with hepatic disorders and ovarian tumors showed values of the same order of magnitude (Figures 1 and 2).

In evaluating the specificity and sensitivity of the two RIA procedures we used for CA 125 (Abbott and Cis), we tested sera from 57 of the cancer patients (16 of them with ovarian cancer) and 118 patients with benign chronic diseases. As measured by the Abbott assay, serum CA 125 was increased (>35 U/mL) in 69% of the ovarian cancer patients studied, 44% by the Cis assay (Figure 2). In the group of chronic non-neoplastic diseases, increased values in CA 125 were measured by both RIAs in those with hepatic pathology, particularly for the icteric cirrhotic patients (eight of nine). Fewer patients with icteric noncirrhotic (n = 23) and cirrhotic nonicteric (n = 14) disease showed increased CA 125 with the Cis procedure (30% and 43%, respectively) than with the Abbott system (44% and 50%, respectively). Patients with renal failure (n = 19) or undergoing chronic dialysis (n = 46) showed a comparable incidence of increased values as measured with either kit (10% for Abbott, 11% for Cis). No increases in CA 125 were observed in the seven diabetic patients.

Figure 3 shows plots of receiver operating characteristic curves for determining the changing sensitivity and speciﬁcity of the assays at various cutoff values. The Abbott CA 125 assay was more sensitive for ovarian tumors than was the Cis CA 125 assay at cutoff values <100 kU/L; however, the percentage of false-positives was also higher with the Abbott kit. The percentage of false-positives in the hPLAP assay is lower than that for either CA 125 assay system.

Discussion

Tumor-marker assay may be helpful for detecting recurrent diseases and for monitoring tumor activity in patients with advanced gynecological malignancies (6, 9), but there is no reliable tumor marker for the primary diagnosis of the vast majority of ovarian cancers (10, 11). CA 125 is considered a potential clinically useful marker for monitoring patients with epithelial ovarian cancer (2, 7, 9).

When we used a cutoff value of 0.1 U/L for hPLAP, according to Pollet et al. (4), 45% of the patient with ovarian cancer had increased hPLAP in their serum. To obtain the same sensitivity for CA 125, the corresponding cutoff was 65 U/mL for the Cis kit and 100 U/mL for the Abbott kit. The

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Table 1. Concentrations of hPLAP, CA 125, and CEA in Serum

<table>
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<tr>
<th>Pathology</th>
<th>n</th>
<th>hPLAP &gt;0.1 U/L, * no. (and %)</th>
<th>&gt;35 kU/L, * no. (and %)</th>
<th>&gt;60 kU/L, * no. (and %)</th>
<th>CEA &gt;8.4 μg/L, no. (and %)</th>
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CA 125 assayed with kit from International Cis, St. Quentin-Yvellines, France.

* Cutoff value shown representing the 99th percentile of a hospital population.

* Cutoff value shown representing the 99th percentile of normal blood donors.

* Arbitrary cutoff value of Bast et al. (2).
The tumors 125 changing (2) differ correspondingly and the corresponding values used for 125 as in Fig. 1. The 65 kU/L cutoff value for 125 is the arbitrary value used by Bast et al. (2)

Fig. 2. Comparison of hPLAP and CA 125 in sera of patients with ovarian tumors, as evaluated with Cis CA 125 RIA (n = 20) or Abbott CA 125 RIA (n = 16) and hPLAP ELISA. Cutoff values for hPLAP and CA 125 as in Fig. 1. The 65 kU/L cutoff value for CA 125 is the arbitrary value used by Bast et al. (2)

corresponding specificity, however, at these cutoff values differed markedly for the two antigens: 98% for hPLAP and approximately 80% for both the Cis and the Abbott CA 125. At accepted cutoff values (0.1 U/L for hPLAP; 5 U/mL for CA 125) the sensitivity of CA 125 assay exceeds (Abbott) or equals (Cis) that of hPLAP, but hPLAP is far more specific.

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References


