Comparison of Portal and Peripheral Blood Levels of Carcinoembryonic Antigen, CA 19-9, and CA 125 Tumor-associated Antigens in Patients with Colorectal and Pancreatic Cancer


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ABSTRACT

Synchronous serum specimens from the systemic and portal circulation of 43 patients with gastrointestinal cancer were assayed for levels of carcinoembryonic antigen, CA 19-9, and CA 125 tumor-associated antigens. The number of patients having a mean ratio of portal to systemic levels >1 and the observed quantity of tumor-associated antigens were significant for carcinoembryonic antigen and CA 125 only in patients with colorectal cancer. No correlations were noted with the surgical stage of disease or with high or low (normal) levels of the three tumor-associated antigens. These findings suggest that peripheral concentrations of these antigens are in equilibrium with shedding from tumors and that hepatic clearance of a single pass does not significantly alter peripheral concentrations.

INTRODUCTION

Thomas and coworkers (1, 2) studied hepatic clearance of CEA (3) in experimental models and found the serum half-life of CEA to be as short as 3 min. After resection of liver secondary lesions, CEA with a half-life between 3 and 10 h (4) was cleared from the circulation of patients. In patients with benign liver disease, systemic and portal blood levels of CEA were not significantly different (5). Thomas and Zamcheck have proposed inhibiting hepatic uptake of CEA in order to more accurately measure its input into the general circulation (6). To investigate this premise in humans, portal and peripheral blood was sampled synchronously and assayed for CEA, CA 19-9 (7), and CA 125 (8) prior to resection of primary colorectal and pancreatic tumors.

MATERIALS AND METHODS

Patients. Twenty-three patients with primary colorectal cancer, 11 with primary pancreatic cancer, 9 with colorectal liver metastases, and 5 with metastatic tumors were studied (one patient was studied during resection of the primary and again during resection of the liver metastases). Six ml of blood were drawn synchronously from the portal circulation and from an artery or vein in the arm of the patient. Blood was drawn from the draining mesenteric vein of colorectal cancers prior to its ligation and by needle puncture of the portal vein in all other patients. Preoperative and 24-h postoperative peripheral samples were also obtained. Serum samples were stored at -20°C until assayed. Hematocrits of paired portal and peripheral samples were measured to allow for possible dilution of peripheral blood by i.v. infusions.

Assays. Sera were analyzed in duplicate and in one batch assay to eliminate interassay variation. CA 125 was assayed as described by Bast et al. (9), and CA 19-9 using the modified (10) immunoradiometric forward sandwich assay was as described by Del Villano et al. (11). These assays were supplied in kit form by Centocor (Malvern, PA). CEA was assayed by an immunoradiometric sandwich technique using monoclonal antibodies provided in kit form by Abbott Laboratories (Chicago, IL).

Results were expressed as the ratio between serum levels of the cancer-associated antigen in portal blood compared with peripheral blood. The number of patients with portal levels higher than peripheral levels was analyzed statistically by the sign test (12). Confidence levels for the mean ratios were determined based on a t statistic, and levels above and below the reference values were compared by a two-sided t statistic.

RESULTS

The 24-h preoperative levels of the three markers were within the experimental "within assay" error of the intraoperative systemic levels. The hematocrits were similar for the paired intraoperative specimens, so there was no dilution effect to account for any observed differences in marker levels in the synchronous samples. The number of patients having portal/mesenteric levels higher than the systemic was about 30% and significant for CEA and CA 125 but not CA 19-9.

The mean ratios for each marker in the three patient groups are depicted in Table 1. Only the group with colorectal carcinoma has enough patients for meaningful statistical analyses. These ratios were greater than 1 significantly more often than they were less than 1 (sign test, P = 0.001 for CEA and 0.008 for CA 125) (12). The observed quantitative levels are significantly higher in the portal circulation than the systemic for CEA (P = 0.003) and CA 125 (P = 0.03) when compared using a t test (two sided). The nine patients with liver metastases have the same preponderance of higher portal levels of CA 125 and, to a less and nonsignificant extent, of CEA as well. The data were also analyzed for possible differences in the synchronous specimens depending on whether they were above or below the previously established reference values of 5 ng/ml for CEA, 40 units/ml for CA 19-9 (7), or 35 units/ml for CA 125 (4). The results of this analysis indicate that there are no significant differences dependent on either high or low amounts of the three antigens secreted. Similarly, the data were examined for possible correlations with surgical/pathological stage of disease, and no significant relationships were observed with any Dukes' stage nor in patients with early (Dukes' A and B1) cancer versus nine patients with liver metastases. It is worth emphasizing that, of these nine patients, five were scheduled for a curative resection, and the liver metastases observed at surgery did not constitute a significant or major proportion of the tumor burden. One further patient whose systemic level of CEA was insignificantly higher than that in the portal vein had a significant tumor load in the liver and was restudied during resection of the liver metastases 2 mo later. On this occasion, both CEA and CA 19-9 levels had increased 3-fold, but the CA 125 levels were decreased by 60%. The portal/systemic ratios in the presence of significant hepatic tumor burden were as follows: CEA, 1.10; CA 19-9, 0.95; and CA 125, 1.09. However, these ratios do not suggest any real differences from unity.
Cancer relates to the sampling sites; blood was drawn directly clonal antibodies versus CEA. This does not seem to be a CEA assay, it is possible that the specificity of the MoAb used et al. (13) and Lokich et al. (4). Maintenance of this equilibrium between tumor shedding and hepatic metabolism of these an are maintained in a steady state by a dynamic equilibrium with colorectal carcinoma, particularly the patients with colon determinants.

Despite the rapid clearance of CEA and other glycoproteins by the liver in experimental models, it appears that the peripheral concentration of CEA, CA 19-9, and CA 125 in humans is in equilibrium with tumor shedding. Moreover, even in patients with significant hepatic tumor burden or those with very high levels of these antigens, liver clearance does not mask antigen production by tumor. Therefore, attempts to increase peripheral levels of these antigens by manipulating hepatic clearance would seem an unlikely strategem to facilitate the early detection of antigen-secreting cancers.

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REFERENCES

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