Gamma-Glutamyl Transpeptidase in Cancer Diagnosis

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ABSTRACT

Serum gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP) and aspartate aminotransferase (AST) were assayed in patients with cancer. GGT was more sensitive than either ALP or AST in detecting metastatic carcinoma to the liver in both icteric and anicteric patients with cancer. Extremely high activities of GGT were seen in patients with hepatoma, carcinoma of the pancreas and of the gallbladder. In patients with metastatic carcinoma to the bone, serum ALP was uniformly elevated, but GGT was either normal or only modestly elevated compared to ALP. Abnormally high elevations in GGT activity in patients with cancer is strongly suggestive of hepatic involvement.

Introduction

Elevations in gamma-glutamyl transpeptidase (GGT) appear to be specific for hepatobiliary-pancreatic disease. Increases in GGT activity have been described in various hepatic and pancreatic disorders, including viral hepatitis, chronic hepatitis, cholelithiasis, cholecystitis, cirrhosis, fatty liver, cholangitis, metastatic carcinoma to the liver and pancreatitis. In addition, elevations have also been seen in epilepsy and in brain tumors and following myocardial infarction. In cancer patients, increased GGT activity is the most sensitive indicator of liver involvement by cancer. An investigation of cancer patients was undertaken to determine the value of GGT assays in this group. In addition to the assay of GGT, alkaline phosphatase (ALP; orthophosphoric monoester phosphohydrolase E.C. 3.1.3.1), and aspartate aminotransferase
Materials and Methods

The patient population consisted of a total of 98 patients with the diagnosis of cancer at the Columbia-Presbyterian Medical Center, New York. The patients were selected with the aid of a computer which listed admitting diagnosis. After performing the enzyme assays, the patients' charts were reviewed.

Serum specimens were drawn from clinic patients and in-patients. Specimens were processed within two hours after collection; ALP, AST and total bilirubin were determined within 24 hours after collection. GGT activity was determined between two to seven days after collection. All specimens were stored at 4°.

GGT was measured kinetically at 30° on the Abbott ABA-100 Bichromatic Analyzer® by the method of Szasz,17 with 1-gamma-glutamyl-p-nitroanilide as substrate. Alkaline phosphatase activity was determined at 37° on the SMA 12/60† using p-nitrophenol phosphate as substrate.9 AST [uv assay]5 and total bilirubin3 were determined on the SMA 12/60.

Results

The results are summarized in figures 1 to 5. Since the distribution of GGT activity in normal patients does not follow a gaussian distribution, the frequency distribution of GGT assays for normal patients (total of 100) was plotted and the upper limit of normal (98 percent of population) was calculated. This was found to be 45 U per l at 30° which was set as the upper limit of normal. The upper limit of normal for AST

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† Technicon Corp., Tarrytown, NY 10591.
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was set at 50 U per l and for ALP at 85 per l.

Because of the diverse range of absolute values for the enzymes studied, we have chosen to express the results as "times (×) upper limit of normal" (×ULN), in order to facilitate comparisons among the various enzyme assays. Each figure shows the three enzymes assayed, the relative elevation in each (plotted on a logarithmic scale) and expressed as ×ULN and the absolute number and percentage of patients with elevations for each enzyme.

In figure 1 are summarized the results for 34 patients with cancer but with no clinical, biochemical, or radiological evidence of hepatic metastases. Only 4/34 or 12 percent of the patients displayed a modest elevation in serum GGT activity (less than 2 ×ULN), while 7/34 or 21 percent of the patients had slight elevation in serum ALP.

In figure 2 are displayed the results for patients with carcinoma with metastases to bone. All 15 patients had increased ALP activity, often to spectacular levels (one case of disseminated prostatic carcinoma to bone had an absolute ALP of 5,210 U per l or 61.3 × ULN). In contrast, although GGT was modestly elevated in 4/15 cases (27 percent), this elevation was not proportionately increased to the same extent as ALP. Serum AST was elevated in 3/15 (20 percent) of patients.

In figure 3 are contained the data for patients with hepatoma, carcinoma of the pancreas and carcinoma of the gallbladder. Precisely 4/9 or 45 percent of cases in this group had ALP activities exceeding 8.0 × ULN, whereas 7/9 or 78 percent of patients in this group had values of GGT activity greater than 8.0 × ULN. In contrast only one AST value exceeded 5.0-fold, the upper limit of normal, while 33 percent of AST activities were within normal limits.

![Figure 3. Summary of results for 9 patients with hepatoma, carcinoma of the pancreas and carcinoma of the gall bladder.](image)

![Figure 4. Summary of results for 18 icteric patients with biopsy-proven, clinically evident and biochemical or radiological evidence for metastatic carcinoma to the liver.](image)
In figure 4 are summarized the data for icteric patients with biopsy-proven, clinically evident and biochemical or radiological evidence for metastatic carcinoma to the liver. Icterus in patients was defined as cases in which the total bilirubin exceeded 1.5 mg per dl. In 90 percent of these patients, GGT activity was increased from 5.0 × ULN to as high as 60 × ULN, whereas the ALP activity was less strikingly elevated. AST was either only moderately elevated, usually less than 5.0 × ULN, or normal.

In figure 5 are summarized the data for anicteric patients with metastatic carcinoma to the liver. Over 50 percent of the patients in this group had GGT activities exceeding 5.0-fold, the upper limit of normal. On the other hand, only 50 percent of patients had ALP activities greater than 3.0 × ULN.

### Discussion

GGT was usually normal in patients without metastatic carcinoma to the liver, although modest elevations of GGT were found in a few patients. ALP was observed to be modestly elevated in the same small group of patients.

In patients with known metastatic carcinoma to the bone with no liver involvement, striking elevations of ALP were observed in all 15 cases studied. The rise in ALP was disproportionate to the modest elevation of GGT, indicating a probable osteoblastic source for the increase in nonspecific ALP. However, in some cases the GGT was moderately elevated (up to 2 × ULN) which may indicate occult hepatic metastases or an alternative source for the increase in GGT. Recently, Rosalki reported high GGT activity in seminal fluid and suggested that in patients with prostatic carcinoma, the increase in GGT may originate from prostatic tissue. Increased GGT in patients with disseminated carcinoma to bone can only be resolved at the time of autopsy when a thorough search of the liver can be conducted. In the author’s experience, however, the disproportionate rise in ALP with a normal or only modestly elevated GGT indicates metastatic carcinoma to bone without hepatic involvement.

Abnormally high GGT activity is found in patients with hepatoma and carcinoma of the pancreas and gallbladder. Thus, 7/9 or 78 percent of patients in this group had values of GGT exceeding 8.0 × ULN, whereas only 4/9 (45 percent) of patients in this group had ALP activities greater than 8.0 × ULN. AST proved to be the least sensitive indicator of primary pancreatic, hepatic or biliary neoplasm, with no values exceeding 5.0 × ULN and with 33 percent of the values being normal.

In patients with metastatic carcinoma to the liver with jaundice, 16/18 or 89 percent had GGT activities exceeding 5.0 × ULN, 50 percent with GGT values greater than
10 × ULN. In contrast ALP was less strikingly elevated, with 14/18 (78 percent) having ALP values in excess of 5.0 × ULN, and 6/18 or 33 percent with ALP activities exceeding 10 × ULN. AST was much less sensitive in detecting metastatic carcinoma to the liver, with 50 percent of the patients falling between 2–5 × ULN and only 3 patients exceeding 5.0 × ULN.

In anicteric patients increased GGT activity was a sensitive indicator of hepatic metastases. In 100 percent of patients GGT activity was elevated, with 14/22 (64 percent) of patients having GGT activity in excess of 5.0 × ULN. Also, 17/22 or 77 percent of patients had AST assays 2.0 × ULN falling between 2–5 × ULN, highlighting the lack of sensitivity of AST for detecting hepatic metastases.

Increased GGT activity proved to be a good indicator of metastatic carcinoma to the liver. In patients with cancer, an elevated GGT is strong presumptive evidence of hepatic involvement. GGT proved to be more sensitive than either ALP or AST in detecting liver metastasis, especially in the absence of jaundice. In patients with disseminated carcinoma to bone, GGT was either normal or modestly elevated, in contrast to serum ALP which was markedly increased. GGT is not an absolutely specific or definitive diagnostic enzymatic test for metastatic carcinoma to liver since GGT is also increased in various disorders affecting the liver such as cirrhosis, cholecystitis, granulomas in liver and hepatic abscesses. However, in cancer patients an increased GGT is suggestive of hepatic involvement and should be used in a discriminatory fashion: if there is an elevation in alkaline phosphatase, the abnormal increase should be followed up by an assay for GGT which will indicate the source of the non-specific elevation in ALP.

References


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