Concentrations of Tumor-Associated Trypsin Inhibitor and C-Reactive Protein in Serum in Acute Pelvic Inflammatory Disease

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We measured tumor-associated trypsin inhibitor (TATI) and C-reactive protein (CRP) in serum of 29 patients with proven pelvic inflammatory disease (PID). TATI values were increased in seven (24%), paralleling increases in CRP. TATI was increased by about 3.5-fold in seven of eight patients with CRP concentrations >90 mg/L, but in none of 21 patients with CRP concentrations <90 mg/L. TATI concentration and severity of PID as determined by laparoscopy or endometrial biopsy were not correlated. These results suggest that, in severe infections, regulation of TATI synthesis resembles that of acute-phase proteins.

Microbial invasion, tissue injury, and acute inflammation turn on the acute-phase response in the host. During the response, the liver increases the synthesis of certain acute-phase proteins. Of these, C-reactive protein (CRP) is most widely measured in clinical practice. Acute pelvic inflammatory disease (PID) is a polymicrobial infection with a wide range of symptoms and signs. Determination of CRP in serum has hastened the diagnosis of PID (1).

In a previous study (2) we demonstrated a high prevalence of above-normal concentrations of ovarian cancer antigen CA 125, but not of other tumor markers (CEA, AFP, CA 15-3, β2-microglobulin), in patients with proven PID. Values for CA 125 were correlated with severity of PID, but not with CRP in serum. We have now studied the correlation between CRP and another marker for ovarian cancer, tumor-associated trypsin inhibitor (TATI) (3). TATI, a 6-kDa peptide, is immunologically identical to the pancreatic secretory trypsin inhibitor (4, 5). Its concentrations are high in serum in all cases of mucinous ovarian tumors and in some serous tumors (6). However, its concentrations may also be increased in bronchitis (3) and hepatobiliary obstruction (7). In patients with various nonmalignant gynecological disorders—including mild infections—TATI concentrations are not increased (8). Patients with severe gynecological infections have not been studied yet. We now report a relatively high prevalence of high values for TATI in serum of patients with proven PID, and a strong nonlinear correlation between TATI and CRP.

Materials and Methods

Study population. The study population consisted of 29 women with acute PID seen in the Department of Obstetrics & Gynecology, University Central Hospital, Tampere, between June 1983 and June 1984. All were hospitalized and underwent laparoscopy and endometrial sampling as detailed elsewhere (9).

Definition of endometritis and salpingitis. The histopathological diagnosis of endometritis was based on the identification of plasma cells (9). The severity of plasma-cell endometritis was graded into mild, moderate, or severe on the basis of histopathological criteria (10). The presence of salpingitis was assessed by laparoscopic criteria and classified as mild, moderate, or severe (11). The minimum criteria for salpingitis were the presence of erythema and edema of the fallopian tubes, with mucopurulent exudate expressed from the fimbrial end of the tubes.

Collection of specimens. Collection of culture specimens for isolation of specific microorganisms from the vagina, cervix, and the upper tract was done as detailed elsewhere (9). Endometrial biopsy specimens were fixed in formalin and processed by routine histological methods. Sera were sampled at the time of admission and again at the time of discharge.

Other procedures. Procedures for isolation of specific microorganisms have been previously described in detail (9). TATI in serum was measured by RIA (3). The mean concentration of TATI in serum of healthy men and women is 11 µg/L; the normal reference interval is 3 to 21 µg/L (3). Thus, we used a cutoff of 22 µg/L. Serum CRP was

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measured turbidimetrically (12) with reagents from Orion Diagnostica, Helsinki, Finland. The cutoff value for CRP was 12 mg/L.

Fisher’s exact test was used for statistical comparisons.

Results

Of the 29 patients, 19 (66%) had supranormal values for serum CRP and seven (24%) had supranormal values for serum TATI. CRP was increased in two (40%) of five patients with endometritis only, in seven (54%) of 13 patients with mild salpingitis, in six of seven patients with moderate salpingitis, and in all of four patients with severe salpingitis. Values for CRP correlated positively with severity of proven PID (Figure 1). TATI concentrations in serum were above normal in one of five patients with endometritis only, in three of 13 patients with mild salpingitis, in one of seven patients with moderate salpingitis, and in two of four patients with severe salpingitis. Thus, there was no clear-cut correlation between TATI concentration and severity of proven PID.

TATI was above normal in seven of eight patients with a CRP concentration >90 mg/L, but in none of 21 patients with a CRP concentration <90 mg/L (P = 0.002 by Fisher’s exact test, Figure 1). The correlation between values for CRP and TATI was not linear, but rather suggested a threshold response (Figure 2). TATI values for the seven patients ranged from 25 to 145 µg/L (mean, 74 µg/L). From two patients Chlamydia trachomatis was isolated, from two other patients, Neisseria gonorrhoeae. Three of the eight TATI-positive patients had fever (>37.5 °C) vs only one of the TATI-negative patients (P = 0.05, Fisher’s exact test). All seven patients with increased TATI concentrations in the acute phase had normal concentrations in the convalescent phase (range 10 to 16 µg/L). A second laparoscopy, performed approximately four months after the index episode, showed tubo-ovarian adhesions in three of six TATI-positive patients vs only two of 17 TATI-negative patients.

Discussion

Several tumor-associated proteins are used as biochemical markers for ovarian carcinoma and other malignancies. One of the markers mainly used for gynecological cancer, CA 125, may become increased in benign gynecological conditions as well (13–15). We now show that another marker for gynecological cancer, TATI, may also become increased in severe gynecological infections. However, the mechanisms behind the increases in these two markers may differ. The increase in TATI, but not CA 125 (2), was associated with an increased concentration of CRP. This supports the idea that TATI in some respects resembles acute-phase proteins. This may also be related to the fact that CA 125 and TATI are preferentially associated with different types of ovarian tumors, TATI with mucinous tumors (4, 16) and CA 125 with nonmucinous tumors (17). We found increased TATI in serum of 24% of patients with PID, and increased TATI concentrations were invariably associated with high values for CRP.

Several studies have demonstrated that the CRP assay is a sensitive and specific augmentary test for the diagnosis of PID (1, 18–20). The ability of microbial substances to stimulate the synthesis of hepatic acute-phase proteins such as CRP appears to be a prominent pathophysiological mechanism in PID. Production of interleukin-1 (IL-1) by cells of monocyte-macrophage origin is a part of the pathological mechanism in many infections, leading to dramatic increases in the synthesis of CRP (21). In our patients, TATI was never increased in connection with moderate increases in CRP. Evidently some additional factor, such as tumor necrosis factor (TNF), is required before the expression of TATI is increased. Induction of one protease inhibitor, α1-antichymotrypsin, in TNF-treated hepatocytes has been described (22). We have recently described a significant correlation between the concentrations in serum of another physiological protease inhibitor, α1-antitrypsin, and TATI in PID patients (23). However, the role of both IL-1 and TNF as the primary inducers of the acute-phase response is still controversial (24). In PID it is likely that: various lymphokines take part in the acute-phase response, their action is not synergistic, and there are complex interactions and feedback mechanisms.

Although the TATI concentrations were clearly increased in PID during the acute phase, they normalized in all cases after the antimicrobial treatment. This was also the case for CA 125 (2). Although there was no correlation between TATI and the severity of PID, increased concentration of TATI seemed to predict tubal damage observed at second laparoscopy. This suggests that acute-phase TATI reflects tissue damage caused by severe inflammation, presumably associated with disruption of the basement membrane. Thus, healing of the inflammation by fibrosis might be more common in TATI-positive than in TATI-negative cases. However, larger prospective studies are needed to find out whether an increase in TATI during the acute episode is a marker of permanent tubal damage.
Lactate Dehydrogenase Isoenzyme Patterns in Serum of Patients with Metastatic Liver Disease

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Total lactate dehydrogenase (LD, EC 1.1.1.27) and LD isoenzymes were determined in serum of 170 patients with metastatic liver disease, 35 of whom had multiple metastatic sites. Overall, values of LD were above normal for 78% of the 170 patients. Half of the patients had an isomorphic pattern of LD isoenzymes (i.e., relative increase in all five isoenzymes); the other half had an increased LD-4,5 pattern, mostly a solitary increase in LD-5 only. Of those patients with normal LD values, 92% had the increased LD-4,5 pattern, whereas 70% of patients with LD values >350 U/L had an isomorphic pattern of LD isoenzymes. All 35 patients with multiple metastatic sites had LD activity >350 U/L; in the majority of them (74%) it was >500 U/L; in 31 (89%), the increase was isomorphic. The diagnostic efficiency of the combined LD >225 U/L (upper limit of normal) and increased LD-4,5 test results was much better than that of LD >225 U/L alone (93% vs 74%). We conclude that serum LD and LD isoenzymes should be determined in every patient with suspected liver metastatic disease. The isomorphic pattern of LD isoenzymes is apparently associated with higher values for total LD and was common among the patients with multiple metastatic sites.

Additional Keyphrases: cancer • multiple metastases • diagnostic efficiency

Lactate dehydrogenase (LD, EC 1.1.1.27), one of the glycolytic enzymes, catalyzes the reversible reduction of pyruvate to lactate in the glycolytic cycle (1). The observation (2-4) that many tumors utilize glucose through the anaerobic pathway and generate a considerable amount of...