Carcinomatous and Tuberculous Pleural Effusions

Comparison of Tumor Markers

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As an aid in the differential diagnosis of exudative pleural effusions, tumor markers were investigated. We measured immunosuppressive acidic protein (IAP), carbohydrate antigen 19-9 (CA 19-9), tissue polypeptide antigen (TPA), carcinoembryonic antigen (CEA), adenosine deaminase (ADA), and alpha,-acid glycoprotein (AGP) in the pleural fluid of 36 patients with carcinomatous pleural effusions and of 35 patients with tuberculous pleurisy because we have frequently found these diseases to be associated with exudative pleuritis. Tuberculous pleural effusions had significantly higher levels of IAP, ADA, and AGP than carcinomatous effusions (p<0.005). On the other hand, CEA, CA 19-9, and TPA were significantly higher in carcinomatous pleural fluids than in tuberculous fluids (p<0.05). There was a correlation between IAP and AGP levels, and their specificity was low. Therefore, combined assays of CEA, CA 19-9, and ADA may be useful in distinguishing pleural effusions due to malignancies from those of tuberculous origin.

Common etiologies of exudative pleural effusions in our experience are carcinoma and tuberculosis. Although confirmatory diagnosis of the cause of pleural effusions is made by pleural biopsy or cytologic or bacteriologic study of the pleural fluid, diagnostic problems are not uncommon. In such cases, determination of various tumor markers in the pleural fluid may be helpful in the differential diagnosis.1,2

Immunosuppressive acidic protein (IAP), described as a subtype of α,-acid glycoprotein (AGP) by Tamura et al.,3 is different from AGP in isoelectric point (IAP, 3.0; AGP, 2.9), molecular weight (IAP, 50,000; AGP, 40,000 to 44,000), and carbohydrate content (IAP, 31.5 percent; AGP, 45 percent). IAP has been found to suppress both phytohemagglutinin-induced lymphocyte blast formation and mixed lymphocyte reaction in vitro. Carbohydrate antigen 19-9 (CA 19-9) has been described as an antigen detected by a monoclonal antibody specific for cells of human carcinoma of the colon4 and has been identified as a sialylated lacto-N-fucopentaose II.5 Tissue polypeptide antigen (TPA) is one of the tumor markers described by Björklund.6 It is a single-chain polypeptide with a molecular weight of 22,000 to 23,000. These three markers have been reported to be increased in the sera of patients with cancer.6,7 To our knowledge, there have been no studies of the significance of IAP, CA 19-9, or TPA in pleural effusions.

We measured IAP, CA 19-9, and TPA, as well as carcinoembryonic antigen (CEA), adenosine deaminase (ADA), and AGP, in carcinomatous and tuberculous pleural effusions and attempted to discriminate between the two groups.

MATERIALS AND METHODS

Pleural fluids obtained from 36 patients with carcinomatous pleurisy and 35 patients with tuberculous pleurisy and confirmed by positive pleural biopsy or bacteriologic or cytologic study of the pleural fluid.
Table 1—Incidence of Positive Tumor Markers in Carcinomatous and Tuberculous Pleural Effusions*

<table>
<thead>
<tr>
<th>Effusion</th>
<th>IAP†</th>
<th>CA 19-9†</th>
<th>CEA†</th>
<th>ADA†</th>
<th>AGP†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinomatous</td>
<td>19/36 (52.8)</td>
<td>17/29 (58.6)</td>
<td>23/33 (69.7)</td>
<td>4/30 (13.3)</td>
<td>14/25 (56)</td>
</tr>
<tr>
<td>Tuberculous</td>
<td>33/35 (94.3)</td>
<td>1/28 (3.6)</td>
<td>0/30 (0)</td>
<td>22/28 (78.6)</td>
<td>24/28 (85.7)</td>
</tr>
</tbody>
</table>

*IAP values above 600 μg/ml, CA 19-9 values above 10 U/ml, CEA values above 5 ng/ml, ADA values above 30 U/L and AGP values above 95 mg/dl were considered positive.

†p<0.05.

pleural fluid were frozen and stored at −20°C until assayed.

There were 23 men and 13 women among the patients with carcinomatous pleural effusions and 21 men and 14 women with tuberculous effusions. Patients with carcinomatous effusions ranged from 32 to 88 years of age, with a mean (± SE) of 63.7 ± 14.4 years, and those with tuberculous effusions ranged from 17 to 86 years of age, with a mean of 49.4 ± 19.0. The former group was significantly older than the latter (p<0.01).

The carcinomatous pleural effusions included 30 primary lung carcinomas (20 adenocarcinomas, four epidermoid carcinomas, three small cell carcinomas, one large cell carcinoma, and two unclassified), five metastatic carcinomas (gallbladder, stomach, colon, parotid gland, and liver), and one malignant lymphoma.

IAP was determined by radial immunodiffusion9 (Saikin Kagaku Laboratory), CA 19-9 by radioimmunoassay (RIA) forward sandwich method (Centocor),10 TPA by RIA double antibody method (AB Sangtec Medical),11 CEA by RIA sandwich method (Dainabo)12 and AGP by radial immunodiffusion (Hoechst). ADA activity was determined as described by Hayashi et al.13

The upper limits of determination of levels of CA 19-9 were 10,000 U/ml.

Groups were compared according to an unmatched t test or χ² test.

**RESULTS**

The mean IAP level in carcinomatous pleural effusions was 603 ± 43 μg/ml (mean ± SE) and was significantly (p<0.005) lower than that in tuberculous effusions (831 ± 34 μg/ml) (Fig 1). IAP values above 600 μg/ml were found in 19 of 36 (52.8 percent) carcinomatous effusions and in 33 of 35 (94.3 percent) tuberculous effusions (Table 1). There was a significant difference between these two figures (p<0.05). There was no relationship of the sex or age of patients in IAP and other parameters.

The mean CA 19-9 level in carcinomatous effusions was 1,333 ± 601 U/ml, which was significantly (p<0.05) higher than that in tuberculous effusions (4.5 ± 0.5 U/ml) (Fig 2). CA 19-9 values above 10 U/ml were found in 17

![Figure 2. Carbohydrate antigen 19-9 (CA 19-9) levels in carcinomatous and tuberculous pleural effusions.](image)

![Figure 3. Tissue polypeptide antigen (TPA) levels in carcinomatous and tuberculous pleural effusions.](image)
FIGURE 4. Carcinoembryonic antigen (CEA) levels in carcinomatous and tuberculous pleural effusions.

of 29 (58.6 percent) carcinomatous effusions and in one of 28 (3.6 percent) tuberculous effusions (Table 1). The difference between these two figures was significant (p<0.01).

The mean TPA level in carcinomatous effusions was 5,223 + 1,680 UIL and that in tuberculous effusions was 1,593 + 438 UIL (Fig 3). There was a significant difference between the two figures (p<0.05). Although TPA values above 10,000 UIL were present in four of 27 (14.8 percent) carcinomatous effusions, and all of 25 tuberculous effusions were below the level, reference level of TPA that could separate carcinomatous from tuberculous effusions was not found.

The mean CEA level in carcinomatous effusions was 19.9 + 3.6 ngl/ml and was significantly (p<0.0001) higher than that in tuberculous effusions (1.5 + 0.1 ng/ml) (Fig 4). CEA values above 5 ng/ml were found in 23 of 33 (69.7 percent) carcinomatous effusions and in none of 30 (0 percent) tuberculous effusions (Table 1). This difference was significant (p<0.01).

The mean ADA level in carcinomatous effusions was 15.5 + 1.9 U/L; this was significantly (p<0.0001) lower than that in tuberculous effusions (42.9 + 3.7 U/L) (Fig 5). ADA values above 30 U/L were found in four of 30 (13.3 percent) carcinomatous effusions and in 22 of 28 (78.6 percent) tuberculous effusions (Table 1), a significant difference (p<0.01).

The mean AGP level in carcinomatous effusions was 98 ± 8 mg/dl and was significantly (p<0.005) lower than that in tuberculous effusions (140 ± 8 mg/dl) (Fig 6). AGP levels above 95 mg/dl were found in 14 of 25 (56 percent) carcinomatous effusions and in 24 of 28 (85.7 percent) tuberculous effusions (Table 1), a significant difference (p<0.05).

Among the above six markers, there was a correlation between IAP and AGP in carcinomatous and tuberculous effusions. No such correlation was observed in other pairs, and these findings indicate that each marker is independently valuable. The incidence of positive tumor markers in these pleural effusions using our arbitrarily defined reference levels is summarized in Table 1.

CEA and CA 19-9 alone have a relatively low sensitivity for detecting malignant effusions. However, the combined use of CA 19-9 and CEA in our study led to more improved sensitivity (25/28; 89.3 percent) in malignant effusions than CEA or CA 19-9 alone, although there was no statistical significance. If we assign a score of 1 for CEA levels above 5 ng/ml, for CA 19-9 levels above 10 U/ml, and for ADA levels below 30 U/L, and consider effusions with a total score of 2 or 3 as carcinomatous, those with a total score 0 as tuberculous, and those with a total score 1 as unclassified, of the 41 cases (malignancy 22 and tuberculosis 19) in which all three markers were measured, 33 (80.5 percent) were correctly diagnosed. Eight cases were unclassified, of which three were carcinomatous and five were tuberculous. We did not
I CARCINOMA TUBERCULOSIS

FICHL6. Alpha,-acid glycoprotein (AGP) levels in carcinomatous and tuberculous pleural effusions. determine chemical markers in pleural fluids when diagnosis of pleural effusions was not confirmed, except in seven cases, of which six were correctly diagnosed and one was unclassified by the combined assay of CA 19-9, CEA, and ADA.

Tamura and others3 reported a definite increase in IAP in 67 percent of serum of all cancer patients. However, because IAP levels were also increased in the serum of patients with suppurative or collagen diseases, IAP appears to be an acute-phase protein similar to AGP. It is considered that the significance of IAP in pleural effusions is identical with that of AGP as IAP cross-reacts with anti-AGP antibody. Our results, which show that IAP and AGP concentrations in tuberculous effusions are higher than those in carcinomatous effusions, indicate that an increase in IAP and AGP is not specific for cancer and that they may not be appropriate as a marker for malignancy. Asseo and Tracopoulos14 indicated that tuberculous effusions had higher orosomucoid (AGP) values than carcinomatous effusions, confirmed by our findings. On the other hand, Rudman and associates15 showed that orosomucoid (AGP) content is significantly higher in carcinomatous pleural and peritoneal effusions than in those of nonneoplastic inflammatory origin, and Agostoni and Marasini16 reported no significant difference in orosomucoid concentrations in effusions of neoplastic origin and those of nonneoplastic inflammatory origin. Because the series by Rudman et al and by Agostoni and Marasini included pyothorax as nonneoplastic inflammatory effusion, their results seem to contradict ours and those of Asseo and Tracopoulos.

DelVillano and Zurawski2 measured CA 19-9 in sera from cancer patients, control patients with benign disease, and healthy individuals, and stated that CA 19-9 provides excellent sensitivity for adenocarcinomas of the pancreas, stomach, and hepatobiliary system. In their study, levels of CA 19-9 above 37 U/ml were found in four of 32 (12.5 percent) lung cancer patients. Our study revealed CA 19-9 levels above 10 U/ml in 58.6 percent of carcinomatous pleural effusions as compared with 3.6 percent in tuberculous effusions. Based on its high specificity (96.4 percent) and the absence of correlation with CEA, CA 19-9 may be useful in differentiating carcinomatous from tuberculous pleural effusions. Combined assay of CEA and CA 19-9 improved sensitivity for detecting carcinomatous effusions.

Menendez-Botet et al9 found an increased concentration of TPA in the serum of 378 of 513 (74 percent) patients with cancer. Among these, nine of ten patients with lung cancer had an increased TPA value. Badger et al,17 who reported on the significance of TPA levels in ascitic fluid, chose 2.5 µg/ml (10,000UIL) as a cut-off point and found that 17 of the 29 (58.6 percent) cancer patients had TPA levels higher than 2.5 µg/ml, and all those with benign disease, including one noninfectious tuberculosis, were below this level. In our study, we found that although TPA levels in carcinomatous effusions were significantly higher than in tuberculous effusions, the reference level of TPA that could separate the two effusions was not present. The reason why the incidence of positive TPA content in carcinomatous effusions was low compared with that of Badger et al is unknown. Based on our study, there appears to be little clinical need to determine TPA levels in pleural effusions.

Numerous studies of CEA levels in pleural fluid have revealed that carcinomatous fluids have higher levels of CEA than pleural fluids from patients with benign conditions.1,2,12,13,22 Our study also showed increased CEA levels in carcinomatous fluids. CEA level over 5 ng/ml in pleural effusions had a sensitivity of 69.7 percent and specificity of 100 percent as a test for carcinomatous effusions. Determination of CEA values in pleural fluids may be of clinical use as CA 19-9. Since anti-CEA sera used for determination of CEA cross-react with CEA-associated antigens, such as nonspecific cross-reacting antigen23 and normal fecal antigen,24 an increase in CEA levels is not specific for carcinoma in other reported series.25 In our series,
none of the tuberculous effusions had a CEA content over 5 ng/ml. This may be ascribed to the difference of the method for determining CEA.

The ADA activity in tuberculous pleural effusions has been shown to be significantly higher than in carcinomatous effusions.4,10,27 Our results confirmed this finding. At present, there is no other chemical marker that suggests a tuberculous effusion. Although IAP levels in tuberculous effusions were higher than in malignant effusions, IAP has a low specificity for tuberculous effusions (47.2 percent).

CA 19-9, CEA, and ADA appear to be useful as chemical markers for differentiating carcinomatous pleural effusions from tuberculous effusions because of their high specificity. Although the etiologies of exudative pleural effusions are diverse, we conclude that combined assays of CA 19-9, CEA, and ADA are useful in differentiating carcinomatous pleural effusions from those of tuberculous origin because of the low incidence of false-negative (sensitivity 80.5 percent) and false-positive findings and their independence.

REFERENCES


