Thyroid Autoantibodies and Thyroid Function in Patients with Pancreatic Adenocarcinoma

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Pancreatic adenocarcinoma (PA) patients often present high serum titres of several autoantibodies including autoantibodies against β-islet cells and insulin. In the present study we examined with an hemagglutination method the sera of 33 patients with PA for the presence of both anti-mitochondrial and anti-thyroglobulin antithyroid autoantibodies (ATA). Twenty-six surgical patients with other non-malignant gastrointestinal tract (GI) disease (chronic pancreatitis or hernia) and 40 healthy volunteers were used as controls. Eight of the 33 PA patients were found to have ATA autoantibodies, whereas only one patient with chronic pancreatitis and 2 normal individuals had high serum ATA titres. The difference between the PA patients and either of the control groups was statistically significant ($p < 0.05$). The production of autoantibodies could be attributed to impaired immunoregulation caused by the malignant cells.

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Adenocarcinoma of the pancreas is the fifth leading cause of cancer in the Western countries and an almost uniformly fatal disease. Early diagnosis of non-metastatic cancer, however, may have a more favourable outlook (1). Unfortunately, despite advances in diagnostic imaging, most pancreatic cancers continue to be recognised at a late stage, whereas screening asymptotic persons with serum tests and/or ultrasound have been disappointing (2). Such a screening will be cost-effective only in a cohort with a high probability of pancreatic cancer.

Cancer patients often present signs and symptoms not directly related to their malignant lesion. These symptoms may be due to paraneoplastic syndromes caused by biologically active proteins produced by the tumour cells, such as hormones and growth factors. Some of the symptoms may also be caused by autoantibodies (3). The antibodies may be produced because of dysfunction of the regulatory mechanisms of the immune system, by polyclonal activation of the B lymphocytes by the malignant cells or, by disorganisation of the idiotypic network (4). The latter is seen more frequently in patients with haematological malignancies, such as lymphoma and multiple myeloma, and sometimes, these autoantibodies can be used for the follow-up of the disease (5).

In the present study we investigated the thyroid function and the presence of antithyroid antibodies (ATA) in patients with pancreatic adenocarcinoma (PA). We also attempted to correlate the presence of ATA with the prognosis of these patients. As far as we know this is the first study of this kind.

MATERIAL AND METHODS

Our study included three groups:

a) Thirty-three patients with newly diagnosed and histologically confirmed, exocrine pancreatic adenocarcinoma (PA) (17 men and 16 women) aged 40–82 (mean 63.8 years). The malignant tumours were classified and graded using established histopathological criteria and the surgical staging system based on the TNM classification, as follows: stage I: 1 patient, stage II: 3 patients; stage III: 11 patients and stage IV: 18 patients.

b) Twenty-six surgical patients with other non-malignant gastrointestinal (GI) tract disease. Of these patients 14 had cholelithiasis and 12 hernia. They were randomly selected and their age ranged from 39 to 72 years with mean age 61.2 years.

c) Twelve patients with chronic pancreatitis (6 men and 6 women) aged 42–79 (mean 62.5 years).

d) Forty healthy blood donors; 25 males and 15 females with an age ranging from 19 to 76 years (mean 62 years).

None of either the patients or the controls had a previous history of autoimmune disease, or of any disease conceivably associated with autoantibodies, or was receiving any drug affecting the function of the immune system. All participants gave their written informed consent before

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entering the study. Blood samples were collected before any treatment, were drawn among 8 and 10 a.m., serum was separated, frozen at −20°C and blindly analysed.

The following tests were performed: a) Detection of autoantibodies against thyroglobulin (anti-T) and against microsomes (anti-M). We used the method of semiquantative estimation of Bayden with passive hemagglutination. The Kits Thymune-M-T were obtained from Wellcome Diagnostics (London, UK) and the technique applied was according to the instructions of the company. b) Quantitative estimation of T3, T4 and TSH with the use of the RIA technique. The kits were obtained from Allergo (Italy) for T3 and T4 and from Nichols Diagnostics (U.S.A.) for TSH.

Statistical analysis

For the evaluation of the presence of autoantibodies between the groups studied the χ^2, Yate's corrected, test was used. For the correlation of the survival mean values between the subgroups of antibody positive and negative PA patients the student's t-test was used.

RESULTS

Thyroid antibodies

Eight out of 33 (8/33 25%) patients with PA were found to have ATA autoantibodies. Of these, five patients had autoantibodies against microsomes only, two against thyroglobulin only and one against both antigens (Table).

Two of the 40 healthy controls (5%) had also ATA antibodies: one against thyroglobulin and one against both. Only one of the 12 patients with chronic pancreatitis (1/12, 8%) had autoantibodies against thyroglobulin and one of the 26 patients with non-malignant GI tract disease (1/26, 4%) had autoantibodies against both thyroglobulin and microsomes. The difference in the overall incidence of autoantibodies between the pancreatic cancer patients and the controls was found to be statistically very significant ($p < 0.01$). The difference between pancreatic cancer patients and healthy controls was also found to be significant ($p < 0.03$).

No statistical significance difference was found in the prevalence of ATA among the stages of the PA patients examined. Nevertheless, the patients with detectable serum titers of either of the autoantibodies examined had a worse outcome compared with the group of patients without detectable autoantibodies titers: the survival of the first group of patients was 9.4 months ± 0.9 (mean ± SD), compared with 11.8 months ± 1.1 (mean ± SD). The difference was statistically significant ($p < 0.01$).

Thyroid function tests

Thyroid function tests were of no difference in the subgroups studied. The values of T3, T4 and TSH were within the normal range. Only in one pancreatic cancer patient the T3 and T4 values were bellow the normal levels. This patients had high TSH levels, excluding the possibility of euthyroid sick syndrome. One healthy control had also low T3, T4 and high TSH levels suggesting subclinical hypothyroidism.

DISCUSSION

The existence of detectable autoantibodies in the serum of cancer patients has already been described in the past (9–11). There have also been several attempts to produce human monoclonal antibodies by exploiting the properties of lymphocytes from gastric cancer patients, but resulted only in hybridomas producing autoantibodies (12). Furthermore autoantibodies against ssDNA, histones, smooth muscle protein, thyroid antigens and cardiolipin are reported to be increased in many groups of cancer patients (9, 13, 14). Unfortunately, their biologic role is still unclear since the majority of these reports failed to demonstrate any prognostic significance. Nevertheless, there are few studies indicating that the presence of the autoantibodies is of prognostic value in lung and pancreatic cancer (14, 15).

It is now accepted that various malignancies may alter the immune system of the patients and predispose to autoimmune disorders such as autoimmune haemolytic anaemia, neutropenia and thrombocytopenia, and peripheral neuropathies. The production of ATA autoantibodies has been demonstrated in many malignancies including the breast, lung, gastric and colon adenocarcinomas (9, 16–18). There is also evidence of increased risk of pancreatic cancer in hyperthyroid women with a standardized mortality ratio from pancreatic cancer as high as 2.6 (19). In the present study we were able to demonstrate that 23%

Table 1

The prevalance of autoantibodies against microsomes (anti-M) and against thyroglobulin (anti-T) in the various groups of individuals studied

	PA patients	Chron. pancr. patients	Non-malign GI tract dis patients	Normal individuals
Anti-M only	5	0	0	0
Anti-T only	2	1	0	1
Anti-M and anti-T	1	0	1	1
Anti-M or anti-T	8/33 (25%)*	1/12 (8%)	1/26 (3%)	2/40 (5%)

* $p < 0.01$

of the patients with PA had high serum titers of ATA. Their production could be due to impaired immunoregulation caused by the malignant cells, while a polyclonal activation by tumour cells cannot be overlooked. Furthermore, pancreatic cancer may cause specific inflammatory response in the pancreas that could lead to the exposure of otherwise cryptic antigens and induction of the autoantibodies studied. On the other hand, genetic factors may predispose patients to ATA production, since family studies have given support to a genetic basis of autoimmunity (20, 21). Another possible explanation could be that the production of these antibodies is triggered by antigens expressed in the pancreatic neoplastic tissue. In fact, it has been shown in the past that ATA have specific effects on antigens of the islet cell surface, by suppressing in vitro, the glucose-induced insulin release (22). The above observation, as well as our finding could explain the increased incidence of insulin-dependent diabetes mellitus of PA patients (23).

In our study we were able to demonstrate that patients with circulating anti-M and anti-T autoantibodies had a worse prognosis than the group of patients without any detectable autoantibodies. This could be explained by a more intense dysregulation of the immune system observed in these patients. This incident could also be explained by a potential protective role of these autoantibodies to the malignant cells, against the tumour immune response, with the formation of immunocomplexes. Although the number of PA patients that we investigated is relatively high ($n = 33$), yet one cannot definitely conclude that the prognostic value of the autoantibodies studied is independent of the stage of the disease, mainly because of the small number of patients diagnosed at early stages: 4 patients of stages I/II, versus 29 patients of stages III/IV. A stage-associated analysis with larger number of patients is needed for further evaluation of the prognostic value of these autoantibodies in PA.

The diagnosis of chronic thyroiditis is usually based on the presence in the serum of antimicrosomal and/or of antithyroglobulin antibodies in high titer. In the present study, although the incidence of these autoantibodies was quite high (25%), overt or biochemical (subclinical) hypo- or hyperthyroidism was very low. This phenomenon has already been observed in patients with systemic lupus erythematosus (SLE) (24) and in patients with breast cancer and can be attributed to several reasons:

a) The time may have been too short for the development of thyroid disease and longer survival could lead to an increased number of patients with thyroid dysfunction.

b) Some of the tumour-associated autoantibodies may exhibit different binding specifities from those of the primary thyroid disorders. This phenomenon has been shown with antibodies against thyroid peroxidase (18) and with the newly discovered anti-MIC-1 antibody in patients with SLE and hyperthyroidism (25). There have been some reports of coexistence of breast, pancreatic and colon cancer with thyroid disease (26–29), either of the type of Hashimoto thyroiditis (27) or of hypo-, hyperthyroidism (29, 30). However, most frequently the presence of thyroid autoantibodies in gastrointestinal tract cancer patients is reported without the coexistence of thyroid disease (9, 15) and finally,

c) There may be differences in the structure of the autoantibodies since the majority of the antithyroglobulin antibodies in autoimmune thyroiditis are polyclonal while in SLE they are monoclonal (31).

In conclusion, in the present study it is reported, for the first time, the presence of anti-thyroid antibodies in a high proportion of patients with pancreatic cancer without concomitant thyroid dysfunction. The presence of these autoantibodies in cancer patients is indicative of immunologic aberrations. Although they do not cause specific symptoms and syndromes, their presence is correlated with a worse prognosis. Since many questions still seek for their answer our findings form the basis for further investigation, towards the better understanding of the pathogenesis of pancreatic adenocarcinoma.

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