Acta Oncologica Vol. 33, No. 8, pp. 905–907, 1994

THYROID AUTOANTIBODIES AND THYROID FUNCTION IN PATIENTS WITH GASTRIC CANCER

KONSTANTINOS N. SYRIGOS, MANOUSOS M. KONSTANTOULAKIS, MATTHEW CONSTANTOULAKIS, PANAGIOTA MARAFELIA, DIMITRIOS KOUTRAS and BASILIOS C. GOLEMATIS

Antibodies against thyroid antigens are commonly found in patients with chronic gastritis type B (20–30%) and pernicious anaemia (50%), two disorders that predispose to gastric cancer. In addition, thyroid disease in increased incidence has been reported in breast and in colon cancer. In order to determine a) the incidence of antithyroid antibodies (ATA) in gastric cancer, b) the thyroid function in patients with ATA and c) the correlation between ATA and the presence of chronic gastritis, we examined the sera of 32 patients with gastric cancer (GC) for the presence of antithyroglobulin and antimicrosomal antibodies. T_3, T_4 and TSH values were also measured. The sera of 36 patients with malignant tumours of the GI tract other than stomach (OMT) and of 40 healthy blood donors were used as controls. Three of the 32 GC patients had antithyroglobulin antibodies, 4 had antimicrosomal and one had both types. Of the eight patients with ATA (25%) only two had hypothyroidism and another two histologically diagnosed chronic gastritis. Three sera of the healthy controls and one of the OMT had also antithyroid antibodies. To conclude, a significant number of patients with GC had ATA as compared to controls ($p < 0.01$) but the presence of ATA did not necessarily indicate an abnormality of thyroid function. The presence of antibodies did not correlate with chronic gastritis type B.

Cancer patients often present signs and symptoms not directly related to the malignant lesions. 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 (1). 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, finally, by disorganization of the idiotypic network (2, 3). The latter is seen more frequently in patients with haematologic malignancies, such as lymphoma and multiple myeloma, where sometimes it can be used for the follow-up of the course of the disease (4).

In the present study we investigated the thyroid function and the presence of antithyroid antibodies (ATA) in patients with gastric carcinoma (GC) and we attempted to correlate the ATA with thyroid disease or/and with precancerous lesions such as atrophic gastritis and pernicious anaemia.

Material and Methods

The sera from 32 patients with histologically diagnosed GC were used in this study. Twenty-one of the patients were males and 11 females. Their age ranged from 28 to 66 years and the mean age was 45.2 years. The stage of the disease, after the Japanese Surgical Staging for Gastric Cancer, was as follows: Stage I (n = 5), II (n = 7), III (n = 9) and IV (n = 11).

Recieved 10 December 1993.
Accepted 18 May 1994.
From 1st Dept. of Propaedeutic Surgery, Medical School, Athens University (K. Syrigos, M. Konstantoulakis, B. Golematis), Athens Medical Center (M. Constantoulakis), and Dept. of Medicine, Medical School, Athens University (P. Marafelia, D. Koutras) Athens, Greece.
Correspondence to: Dr K. N. Syrigos, Royal Postgraduate Medical School, Hammersmith Hospital, Department of Clinical Oncology, ICRF-Tumour Targeting Laboratory, Du Cane Road, London, W12 0HS, England.

 ISSN 0284-186X

The sera of 40 healthy blood donors were used as controls. Twenty-five were males and 15 females with an age range of 19 to 56 years (mean 42 years). The sera of 36 patients with other malignant tumours (OMT) of the gastrointestinal (GI) tract were also used as controls. Of these patients, 18 had cancer of the colon, 12 pancreatic cancer, 3 adenocarcinoma of the small intestine, and 3 cancer of the liver. All participants were randomly selected and their age ranged from 39 to 62 years (mean 51 years).

The sera of the patients and of the controls were collected before any treatment and were stored at −70°C until tested. The following tests were performed: a) detection of autoantibodies against thyroglobulin and against microsomes and b) quantitative estimation of T_3, T_4 and TSH. For the detection of autoantibodies the method of semiquantative estimation of Bayden with passive haemagglutination was used. The Thymune-M-T kits were obtained from Wellcome Diagnostics and the technique applied was according to the instructions of the company. For the measurement of T_3, T_4 and TSH the RIA technique was used. The kits were obtained from Allergo for T_3 and T_4 and from Nichols Diagnostics for TSH.

All participants were fully informed of the procedure and the purpose of the study and had given their written consent before entering into it.

For the statistical analysis the χ^2-test was used.

Results

Thyroid antibodies. Eight of the 32 patients (25%) with gastric cancer had antithyroid antibodies in high titre in their serum. Of these, four patients had autoantibodies against microsomes, three against thyroglobulin and one against both antigens (Table). Three of the 40 healthy controls (7.5%) also had antibodies: one against thyroglobulin, one against microsomes and one against both. One only of the 36 patients with non-gastric GI tract cancer had autoantibodies against both thyroid antigens. The difference in the overall incidence of autoantibodies between the gastric cancer patients and the control group is statistically significant ($p < 0.01$) using the χ^2-test. The difference between gastric cancer patients and healthy controls was significant ($p < 0.05$) and between gastric and non-gastric cancer patients also highly significant ($p < 0.01$).

Thyroid function tests. Thyroid function tests showed no significant difference between the subgroups studied. The values of T_3, T_4 and TSH were within the normal range. Only in two gastric cancer patients were the T_3 and T_4 values below the normal levels. These patients had high TSH levels, excluding the possibility of euthyroid sick syndrome. One healthy control also had low T_3, T_4 and high TSH levels, suggesting subclinical hypothyroidism.

Discussion

The presence of humoral and cell-mediated specific immunologic reactions in patients with chronic atrophic gastritis and pernicious anaemia suggests that immune mechanism may be important in the pathogenesis of these diseases (5, 6). The most common findings are the presence of antibodies specific for the smooth cytoplasmic membrane of the parietal cells of the stomach. These antibodies are detected in the serum, the gastric juice, and the gastric mucosa of most patients suffering from chronic gastritis or pernicious anaemia and in a high proportion of their relatives (7, 8). Their prevalence is also high in other autoimmune disorders and particularly in thyroid diseases (9, 10).

In the present study, the high incidence (25%, $p < 0.01$) of anti-thyroid antibodies cannot be attributed to pre-existing atrophic gastritis or pernicious anaemia, conditions characterized by high percentage of thyroid antibodies and predisposition of gastric cancer. Only 2 of the 32 patients had histologic evidence of atrophic gastritis and the serum B_{12} was normal in all participants.

It is now accepted that various malignancies may partially alter the immune system of the patients and predispose to autoimmune phenomena (11, 12). It is known that in cancer patients, autoantibodies may cause autoimmune haemolytic anaemia, neutropenia and thrombocytopenia, peripheral neuropathies and other autoimmune disorders (13, 14). The production of autoantibodies could be due to impaired immunoregulation caused by the malignant cells while a polyclonal activation by tumour cells cannot be overlooked. On the other hand, genetic factors may predis-

Table 1

Thyroid autoantibodies in patients and controls

	Patients (n = 32)	Patients with other GI* tumours (n = 36)	Control (n = 40)
Anti-microsomal	4 (12.5%)	0	1 (2.5%)
Anti-thyroglobulin	3 (9.4%)	0	1 (2.5%)
Both	1 (3.1%)	1 (3%)	1 (2.5%)
Either	8 (25.0%)	1 (3%)	3 (7.5%)
Thyroid dysfunction	2 (2.6%)	0	1 (2.5%)

* GI: Gastrointestinal

pose patients to ATA production, since family studies have given support to a genetic basis of autoimmunity (15, 16). Another possible explanation could be that the production of ATA antibodies is triggered by antigens expressed uniquely in the gastric neoplastic tissue. This hypothesis is strengthened by the absence of these antibodies in the group of patients with other malignancies of the GI system.

The diagnosis of chronic thyroiditis is usually based on the presence in the serum of antimicrosomal and/or of antithyroglobulin antibodies in high titre. In the present study the incidence of either type of antibody was quite high (25%) but that of overt or biochemical (subclinical) hypo- or hyperthyroidism was very low. This phenomenon has already been observed in patients with systemic lupus erythematosus (SLE) (17) 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 or follow-up may lead to an increased number of patients with thyroid dysfunction. b) Some of the autoantibodies may exhibit binding specifities different from those of the primary thyroid disorders. This has been shown with antibodies against thyroid peroxidase (18) and with the newly discovered anti-MIC-1 antibody in patients with SLE and hyperthyroidism (19). There have been some reports of coexistance of breast and colon cancer with thyroid disease (20–22), either of the type of Hashimoto thyroiditis (20) or of hypo-, hyperthyroidism (23). However, most frequently the presence of thyroid autoantibodies in cancer patients is reported without the coexistence of thyroid disease and, c) There may be a difference in the structure of the autoantibodies, since the majority of the antithyroglobulin antibodies in autoimmune thyroiditis are polyclonal while in SLE they are monoclonal (24).

In the present study the presence of anti-thyroid antibodies is reported, for the first time in a high proportion of patients with gastric cancer without concomitant thyroid dysfunction. In addition, no association was found between the presence of these autoantibodies and chronic atrophic gastritis or pernicious anaemia. The presence of the autoantibodies in cancer patients indicates the existance of immunologic aberrations. In many cases, however, these autoantibodies do not cause specific symptoms and syndromes and may be inactive or innocent bystanders.

ACKNOWLEDGEMENTS

Financial support was obtained from the university departments involved in the study.

REFERENCES

1. Baylin SB, Mendelsohn GH. Ectopic (inappropriate) hormone production by tumours: Mechanisms involved and the biological and clinical implications. Endocr Rev 1980; 1: 45–8.
2. Nelson DS. Autoantibodies in cancer patients. Pathology 1977; 8: 155–60.
3. Theofilopoulos AN. Immune complexes in cancer. N Engl J Med 1982; 302: 1208–9.
4. Kostiala AA, Gripenberg M, Eloren E, et al. Follow-up of antibodies against single stranded DNA in patients with haematological malignancies. Clin Exp Immunol 1985; 61: 15–23.
5. Whittingham S, Youngchaind U, MacKay IR, et al. Thyrogastric autoimmune disease, studies on the cell mediated immune system and histocompatibility antigens. Clin Exp Immunol 1975; 19: 289–99.
6. Fixa B, Komarkova O, Nozicka A. Leukocyte migration inhibition test with two gastric antigens in pernicious anaemia and in simple atrophic gastritis. Acta Hepatogastroenterol (Stuttg) 1979; 26: 43–5.
7. Irvine WJ, Davies SH, Tertelbaum S, et al. The clinical and pathological significance of gastric parietal cell antibody. Ann NY Acad Sci 1965; 124: 657–91.
8. Varis K, Sumloff IM, Tilikainern A, et al. Gastritis in first-degree relatives of pernicious anaemia gastric cancer patients and controls. In: The genetics and heterogeneity of common gastrointestinal diseases. Academic Press, 1980.
9. Vibo R, Krohn K, Villako K, et al. The relationship of pariental cell, gastric cell and thyroid autoantibodies to the state of the gastric mucosa in a population sample. Scand J Gastroenterol 1984; 19: 1075–80.
10. Misiewicz JJ, Pounder RE, Venable CW. Diseases of the gut and pancreas. London: Blackwell Scient. Pub, 1987.
11. Prehn TR, Prehn ML. The autoimmune nature of cancer. Cancer Res 1987; 47: 927–32.
12. Sela O, Shoenfeld Y. Cancer in autoimmune diseases. Semin Arthritis Rheum 1988; 18: 77–87.
13. Mufti GJ, Figes A, Humblin JT, et al. Immunological abnormalities in myelodysplastic syndrome. Br J Haematol 1986; 63: 143–7.
14. Nobile Orazio E, Marmiroli P, Baldini L, et al. Peripheral neuropathy in macroglobulinaeima. Incidence and antigen-specificity of M-proteins. Neurology 1987; 39: 1506–14.
15. Bottuzo GF, Pajol-Borrell R, Hanafusa T, Feldmann M. Role of aberrant HLA-DR expressions and antigen presentation in induction of endocrine autoimmunity. Lancet 1983; 2: 1113–38.
16. Huminer D, Tomer Y, Pitlick S, et al. Autoantibodies in cancer patients; Are they tumour related or age related? Autoimmunity 1990; 5: 232–3.
17. Kohno Y, Naito N, Saito K, et al. Anti-thyroid antibody activity in sera of patients with systemic lupus erythematosus. Clin Exp Immunol 1989; 75: 217–21.
18. Rasmusson B, Feldt-Rasmusson V, Hegedusa-Perrild H, et al. Thyroid function in patient with breast cancer. Eur J Cancer 1987; 23: 553–6.
19. Salazar Paramo M, Garcia dela Torre I, Hernandez-Vasquez L, et al. Evidence of a new antigen-antibody system (anti-MIC-1) in patients with SLE and hyperthyroidism. J Rheumatol 1989; 16: 175–80.
20. Itoh K, Maruchi N. Breast cancer in patients with Hashimoto's thyroiditis. Lancet 1975; 2: 1119–21.
21. Adamopoulos DA, Vassilaros S, Kapolla N, et al. Thyroid disease in patients with benign and malignant mastropathy. Cancer 1986; 57: 125–8.
22. Rose DP, Davis TE. Plasma thyronine levels in carcinoma of the breast and colon. Arch Intern Med 1981; 141: 1161–4.
23. Bech K, Bliddal H, Feldt-Rassmussen U, et al. Heterogeneity of autoimmune thyroiditis. Allergy 1984; 39: 239–47.
24. Stott D, McLearie J, Neilson L. Analysis of the clonal origins of autoantibodies against thyroglobulin and DNA in autoimmune thyroiditis and SLE. Clin Exp Immunol 1986; 65: 520–3.