Clinical Study on Increased Serum Thyroxine-Binding Globulin in Cancerous State

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Abstract

Serum thyroxine-binding globulin (TBG) in 169 patients with various cancers was determined by radioimmunoassay (RIA). Eleven patients showed a high serum TBG level (>35 µg/ml). Two of them had been treated with estrogen for prostate cancer. One patient had high serum TBG with serum hepatitis. Another 8 cases had normal liver function and also normal levels serum estrogen. Thus, about 4.7% (8/169) of the cancer patients had high serum TBG and mild hyperthyroxinemia caused by unknown mechanisms.

The high TBG level in these patients continued until just before death, or in some cases decreased to normal after removal of cancer tumors by operation.

Cancer is occasionally associated with an increase in serum TBG. Although the mechanism is not clear, the increased TBG in the cancerous state is interesting and has significance as a tumor marker.

Thyroid hormones exist in blood mainly in noncovalent interactions with 3 proteins, thyroxine-binding globulin (TBG), thyroid-binding prealbumin (TBPA), and albumin (Robbins and Rall, 1960; Robbins, 1976; Robbins et al., 1978). These proteins act as the predominant transport proteins, binding more than 99% of the total thyroid hormones (thyroxine and triiodothyronine). Purification of TBG by affinity chromatography with T₄ coupled to agarose (Pensky and Marshall, 1969), anion-exchange chromatography, gel electrophoresis (Korcek and Tabachnick, 1974 and 1976) or gel-filtration (Gershengorn et al., 1977; Robbins et al., 1978) had made possible the development of radioimmunoassay (RIA) for TBG.

An abnormal serum TBG level has been reported in many disease states. Increased TBG in pregnancy is due to an increase in the amount of serum estrogen levels. Increased TBG has been demonstrated in various malignant diseases. Pederson (1974) suggested that TBG might be a “Tumor marker” in patients with primary hepatocellular carcinoma. However, Gershengorn et al. (1976) denied the utility of serum TBG as a tumor marker.

We measured serum TBG and TBPA levels in patients with various cancers, and found a few cases with high serum TBG levels. We report here the thyroid function tests and clinical courses of these patients.
Materials and Methods

Patients in our hospital with various cancers (169 cases) were examined. The diagnosis of cancer was made by physical, biochemical, roentgenological and pathological examination. Blood specimens were obtained after an overnight fast and the sera obtained were stored at -20°C until used.

The following determinations were done on each sample by a commercial radioimmunoassay (RIA) kit: serum TBG from Hoechst lab, carcinoembryonic antigen (CEA) from CIS lab, resin T₃ uptake (RT₃U) and 3, 3', 5'-triiodothyronine (T₃) from Dainabot lab, thyroxine (T₄) from Eiken lab, 3, 3', 5-triiodothyronine (T₂) from Travenol Co, free T₄ (FT₄) from Corning Co, and thyroid stimulating hormone (TSH) from Daiichi RI lab. Determination of serum estrone (E₁), estradiol (E₂), estriol (E₃) and human chorionic gonadotropin (HCG) were performed by Kitasato Biochemical lab.

The TBPA preparation (Hoechst lab) was labelled with ¹²⁵I. The specific activity of the labelled preparation was less than 10 μCi/μg. The assay mixture contained 0.1 ml of ¹²⁵I-TBPA, diluted rabbit antiserum against TBPA (Dako lab, 1:50,000 final dilution), 0.02 ml of test serum (1:150 dilution) in a total incubation medium of 1 ml of 0.1 M phosphate buffer pH 7.8 containing 0.4% BSA (bovine serum albumin) and 0.2% BSG (bovine serum γ-globulin). The mixture was incubated at 5°C for 24 hr, and then the bound and the free fraction were separated by PEG (12.5% at a final concentration). Determination for the sample were performed in duplicate. Usually all test sera were stored in the frozen state until used. The measurable range was between 0.78 and 100 μg/ml of TBPA. The mean recovery of TBPA was 110±8% (mean±SD). The cross-reactivity of the antiserum with other plasma protein was: less than 0.02% of human albumin. The ¹²⁵I-TBG preparation from Hoechst lab and CIS's RIA did not show any cross-reactivity with antiserum for TBPA. The intra-assay and inter-assay were less than 14.1%.

The normal range (mean±2SD) of each RIA method is as follows: TBG: 15-30 μg/ml, CEA; below 10 ng/ml, RT₃U: 25-35%, T₃: 16-40 ng/dl, T₄: 5-11 μg/dl, TSH: 0.8-1.8 ng/ml, FT₄: 1.0-2.3 ng/dl, T₃: 1-10 μU/ml, TSH: 18-34 mg/dl, and E₂: 28-102 pg/ml, HCG: <6.6 IU/1 in normal males and menopausal females.

Results

1) Serum TBG levels in patients with various cancers

Six of 80 patients with gastric cancer (7.5%), 3 of 29 patients with colon cancer (10.3%), 1 of 20 patients with lung cancer (5.0%), 2 of 9 patients with primary liver cancer (22.9%), 1 of 7 patients with breast cancer (14.3%), 1 of 3 patients with uterus cancer (33.3%), both patients with prostate cancer having estrogen therapy, and 2 of 14 patients with other cancers (14.3%) had a higher serum TBG level than the normal controls (Fig. 1).

![Fig. 1. Serum TBG levels in patients with various cancers.](image)

2) Liver function test, serum estrogen and HCG levels of cancer patients with high serum TBG

Liver function, serum estrogen, and HCG were determined in the 11 cancer patients with high TBG (>35 μg/ml). Case 2 suffered from serum hepatitis after gastrectomy. Cases 8 and 9, patients with prostate cancer, were treated with estrogen for more than 6 months. Other patients had normal liver function. Serum estrogen and HCG levels in these 5 patients were in the normal or low range (Table 1).
3) Thyroid function of cancer patients with high serum TBG

Serum TBG levels of 11 patients were 35.4 to 50.1 µg/ml. The highest TBG level (50.1 µg/ml) was found in Case 9, a patient receiving estrogen therapy for prostate cancer. Serum TBPA levels were decreased in 7 cases. T₄ was slightly increased or in the upper range, except for two cases. Free T₄ also was increased in half of the cases and was in the upper range in the remainder. Serum T₃ and rT₃ were at the normal level or slightly elevated. RT₃U was decreased significantly in 8 of 10 cases. Serum TSH was in the normal range in all (Table 2).

Table 2. Thyroid function of cancer patients with high serum TBG level.

4) Changes in TBG, TBPA and thyroid function during the clinical course of cancer patients with high serum TBG

The clinical course of cancer patients without estrogen therapy and without liver dysfunction was examined.

Case 1, a patient with gastric cancer, had subtotal gastrectomy on October, 1979. Serum TBG and T₄ were at a high level for about 8 months and then decreased to the normal range before death (Fig. 2).

![Fig. 2. Change in TBG, TBPA and thyroid function in clinical course of cancer patient (case 1) with high serum TBG.](image-url)
Case 3 was operated on for gastric cancer in May, 1980. Before the operation serum TBG, T₄, FT₄ and T₃ were slightly elevated but normalized after the operation (Fig. 3).

Fig. 3. Change in TBG, TBPA and thyroid function in clinical course of cancer patient (case 3) with high serum TBG.

Case 4 had a recurrence of gastric cancer one year after gastrectomy. Increased serum TBG and decreased RT₃U continued for 6 months until two months before death. Serum T₄, T₃ and FT₄ were always in the normal range (Fig. 4).

Case 10 was diagnosed as having a cholangioma before death, and had an extremely high CEA level (about 500 ng/ml). On autopsy, she was found to have had hepatocellular carcinoma. Hyperthyroxinemia and normal T₃ levels continued for 6 months until one month before death (Fig. 5).

5) Relation between serum TBG and CEA levels in patients with various cancer.

Serum TBG and CEA levels were examined in these patients. There was no relationship between serum TBG and CEA levels. A high TBG was found without any relationship to the CEA level (Fig. 6).
Discussion

It is well known that serum TBG is affected by a few hormones and a wide variety of diseases. Increased serum TBG during pregnancy is well known (Dowling et al., 1956; Robbins and Nelson., 1958) and this phenomenon is caused by increased serum estrogen inducing increased TBG production in the liver (Dowling et al., 1956; Glinoer et al., 1977). Estrogen, especially estradiol, is the most active steroid in this respect (Kagedal and Kallberg, 1977). In the present study we found increased serum TBG in two patients with prostate cancer taking estrogen therapy.

Recently, an elevated TBG level in Graves' patients has been reported by Yabu et al., (1980). In the present study all cancerous patients with a high serum TBG level had neither clinical symptoms of Graves' disease nor anti-thyroidal antibodies.

An acute increase in serum TBG has been reported in infectious hepatitis (Tabei and Shimoda, 1973). In the present report Case 2 showed increased serum TBG during serum hepatitis after a blood transfusion at the time of total gastrectomy. The TBG level normalized following the improvement of liver function.

In the present study we found increased serum TBG in 8 patients without liver dysfunction, without estrogen therapy, and not taking oral contraceptives containing estrogens. Five of these patients showed normal serum estrogen and HCG levels. In a pedigree study of these patients, no congenitally increased TBG trait could be demonstrated.

Previously Pederson (1974) had reported that hepatocellular carcinoma was occasionally associated with an increase in serum TBG. However, Gershengorn et al. (1976) demonstrated that TBG was far from constant and was not correlated with the
serum α-fetoprotein level in hepatocellular carcinoma. We checked the TBG level in 9 patients with hepatocellular carcinoma. Only 1 patient had a high serum TBG level, but α-fetoprotein was in the normal range.

The relation between serum TBG and serum CEA was examined in many cancer patients, but no correlation was found (Fig. 6).

In the cases followed during a clinical course, serum TBG levels in 3 patients (Case 1, 4 and 10) remained high until just before death. The fall may be due to cachexia in the terminal stage of cancer. The serum TBG level in one patient (Case 3) dropped to normal after an operation on the original gastric cancer.

The thyroid function of cancer patients with high serum TBG was examined. Slightly increased serum T₄, T₃, rT₃ and FT₄ were found in some case, but the level of these hormones was normal in half of the cases. The free hormone level and also other thyroid function test results have been reported normal in congenital TBG abnormality (Nikolai and Roberts, 1969). We deduce that the slightly high FT₄ level in the cancer patients may be due to low serum levels of other thyroid hormone binding proteins such as TBPA and albumin, slightly increased serum T₄ or methodological complexities in determining free T₄ accurately.

In the present study we found 8 cases with a high serum TBG level without obvious cause among 169 cancer patients. Although the incidence of elevation is low (about 4.7% of cancer patients), TBG is useful as a tumor marker in certain cancerous states.

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References


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