THERAPEUTIC NUCLEAR MEDICINE

Serum Thyroglobulin, A Monitor of Differentiated Thyroid Carcinoma in Patients Receiving Thyroid Hormone Suppression Therapy: Concise Communication

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Serum thyroglobulin levels were obtained in 86 patients who had undergone thyroidectomy and I-131 ablation for differentiated thyroid cancer, and who were receiving or had recently discontinued thyroid hormone suppression therapy. Excellent correlation was observed between serum thyroglobulin levels in patients receiving thyroid hormone suppression therapy and I-131 imaging studies. Serum thyroglobulin levels equal to or below 20 ng/ml indicate the absence of thyroid carcinoma, and values exceeding 60 ng/ml were indicative of active thyroid cancer but may include some patients without clinical evidence of disease. Intermediate serum thyroglobulin levels were observed in a small number of patients with postsurgical thyroid remnants or active disease. Serum thyroglobulin levels are of considerable value in monitoring the activity of thyroid cancer in patients who are receiving thyroid hormone suppression therapy.

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The determination of serum thyroglobulin (Tg) levels represents an important advance in monitoring the course of patients with differentiated thyroid carcinoma. Serial monitoring of serum Tg after complete thyroidectomy for thyroid cancer can detect residual tumor tissue, metastases, or the recurrence of disease. However, the value of Tg as a tumor marker in thyroid-cancer patients may be influenced by thyroid hormone suppression therapy. If serum Tg levels are to be of clinical value in the follow-up of thyroid-cancer patients, it is desirable to use the assay while patients are receiving thyroid-suppression therapy. This study has been undertaken to evaluate those factors that may be influential in the application of serum Tg as a tumor marker for differentiated thyroid cancer in patients receiving thyroid-hormone therapy. Serum thyroglobulin levels were obtained with a new thyroglobulin radioimmunoassay kit.

PATIENTS

We studied 86 patients (49 F and 37 M) who had undergone thyroidectomy for papillary, follicular, or mixed papillary-follicular thyroid carcinoma. All patients also received I-131 ablation therapy in accord with our previously reported protocol (*1*). After obtaining written consent, blood samples for serum Tg and serum levels of thyroid-stimulating hormone (TSH) were obtained. Blood samples were taken from patients who were receiving thyroid hormone suppression therapy, and again at least 1 mo after such therapy had been discontinued. Scans of the neck and thorax, and whole-body radioactivity surveys, were performed on all patients at 48–72 hr after an oral dose of 5 mCi I-131, using a rectilinear scanner and high-energy focused collimator. Ten patients who had abnormal concentrations of I-131 outside the thyroid bed, or had I-131 concentration in distant metastases, were considered to have active disease and were studied before and after radioiodine ablation therapy.

METHODS

Serum thyroglobulin was determined by radioimmunoassay using a commercial thyroglobulin RIA kit.* The method is a noncompetitive radioimmunoassay procedure (delayed addition method). Rabbit anti-hTg

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TABLE 1. SERUM THYROGLOBULIN DETERMINATIONS (ng/ml) PATIENTS RECEIVING AND NOT RECEIVING THYROID HORMONE

	≤20	21 − ≤60	>60
Active disease	0 (0)*	0 (4)	4 (13)
No disease	96 (61)	13 (14)	1 (1)

* Numbers in parentheses are determinations on patients not receiving thyroid hormone.

TABLE 2. EFFECT OF DISCONTINUATION OF THYROID-SUPPRESSION THERAPY

28 Patients without disease
Average ΔTg = 1.5 ng/ml
Average ΔTSH = 39 μU/ml
Patients with active disease

	On suppression Tg/TSH	Off suppression Tg/TSH
MB	112/4.8	230/37
PM	461/12.3	>1000/98
LS	105/5.6	100/4.7
PZ	110/3.5	144/40

(100 μl) is mixed with 200 μl serum. After 5 hr of incubation at 37°C, 100 μl I-125 hTg is added, and the reactants mixed and left at room temperature overnight. Buffer (100 μl) is then added and mixed before addition of second antibody (200 μl of goat anti-rabbit antibody). After 1 hr of incubation at room temperature, the tubes are centrifuged at 5-10°C for 15 min at 2000 *g*. Supernatants are decanted by inversion and blotting of tubes. Precision is improved by resuspending the precipitates in 2.0 ml of 6% polyethylene glycol in normal saline, then recentrifuging and decanting. Precipitates are counted in a gamma spectrometer. The range of the assay is 5-500 ng/ml, with sensitivity of 2 ng/ml. None of the following proteins showed any significant cross reaction with the anti-human Tg rabbit serum: human AFP, hCG, hPL, hFSH, hPAP, myoglobin. Normal human serum Tg levels do not exceed 60 ng/ml. Thyroid-stimulating hormone was determined by radioimmunoassay using a commerical kit.* Normal range does not exceed 10μU/ml. All blood samples were tested for circulating endogenous anti-Tg antibodies by the tanned RBC-agglutination technique. Since Tg antibodies interfere with the assay, sera containing antibodies were excluded from the study. In the patient population studied, five individuals had Tg serum antibodies.

RESULTS

Patients were separated into two groups depending on whether or not they were receiving thyroid hormone suppression therapy. Serum thyroglobulin levels were segregated in three empirically defined groups as suggested by Echenique et al. (*3*): serum values equal to or less than 20 ng/ml; an intermediate group with serum Tg between 21 and 60 ng/ml: and values exceeding 60 ng/ml.

Table 1 lists the results of thyroglobulin determinations in patients receiving thyroid suppression and in those who were not receiving thyroid hormone. In both groups, thyroglobulin levels usually exceeded 60 ng/ml if the patient had I-131 scan findings indicative of active disease. Patients in both groups who did not have

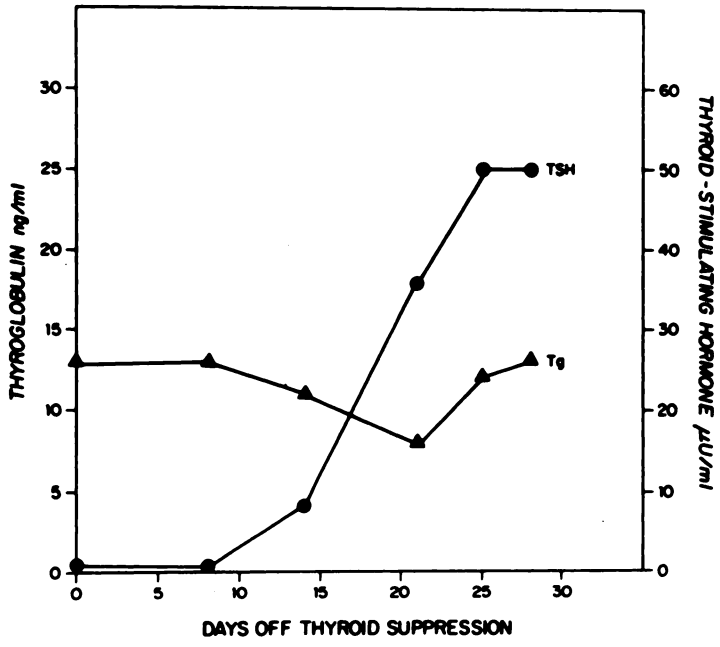

FIG. 1. Changes in Tg and TSH with time in disease-free patient after withdrawal of thyroid-suppression therapy.

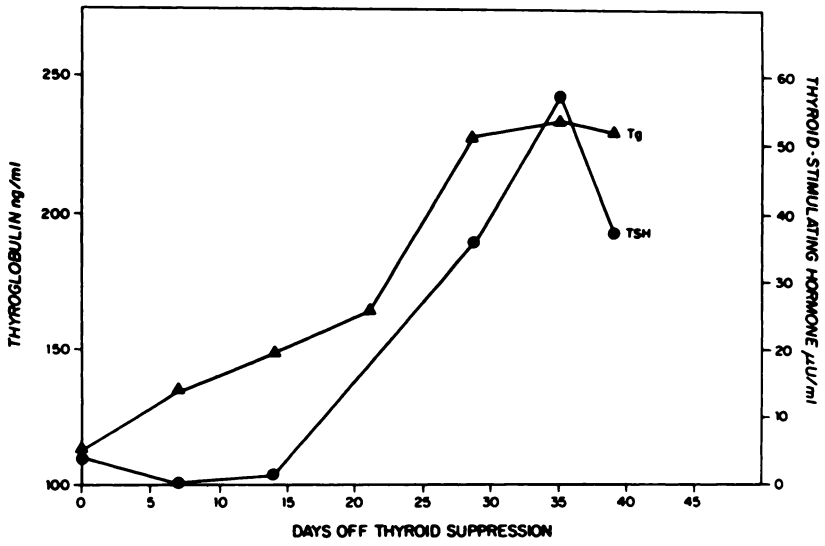

FIG. 2. Changes in Tg and TSH with time in patient with active disease after withdrawal of thyroid-suppression therapy.

positive I-131 scans had thyroglobulin levels ≤20 ng/ml except for a small number whose thyroglobulin levels were in the intermediate range (21–60 ng/ml). Included in the intermediate range were six patients with remnants, but also included were four patients with active disease.

There were no false-negative results in either group. However, two patients gave false-positive results (>60 ng/ml) in spite of concurrently negative I-131 images and no clinical evidence of disease.

Table 2 demonstrates the effect of discontinuation of thyroid-suppression therapy on serum thyroglobulin and thyroid-stimulating hormone levels in 25 patients without evidence of disease. An insignificant rise in thyroglobulin levels was observed in these patients despite a significant rise in TSH levels (Fig. 1). Table 2 also shows the effect of discontinuation of thyroid-suppression therapy in four patients with active disease. In all but one there was a significant rise in both serum Tg and TSH levels (Fig. 2).

The correlations between serum thyroglobulin and I-131 scan findings in thyroid-cancer patients—both on and off thyroid hormone suppression therapy—are shown in Table 3.

TABLE 3. CORRELATIONS BETWEEN SERUM THYROGLOBULIN AND I-131 IMAGES IN PATIENTS BOTH ON AND OFF THYROID HORMONE SUPPRESSION THERAPY*

	On suppression	Off suppression
Sensitivity	1.00	1.00
Specificity	0.87	0.80
Accuracy	0.88	0.84

* Tg >20 was considered positive for statistical analysis.

The presence of postsurgical thyroid-bed remnants measuring 1–3 cm in diameter did not correlate with thyroglobulin levels. Figure 3, A and B shows postoperative scans from two patients. In both cases Tg levels were less than 21 ng/ml.

DISCUSSION

Our study confirms the reports that serum thyroglobulin levels reflect tumor activity in thyroidectomized, I-131-ablated thyroid-cancer patients with differentiated tumor-cell types (*2–15*). The data indicate that tumor activity may be detected readily in patients who are receiving thyroid hormone suppression therapy. Our data also support the concept that serum thyroglobulin levels are under the influence of the pituitary (*7–9,12–14*). However, the discontinuation of thyroid-hormone replacement with concomitant endogenous TSH stimulation appears to enhance serum thyroglobulin levels, primarily in patients with active disease who have high Tg levels (>60 ng/ml). Similar findings have been re-

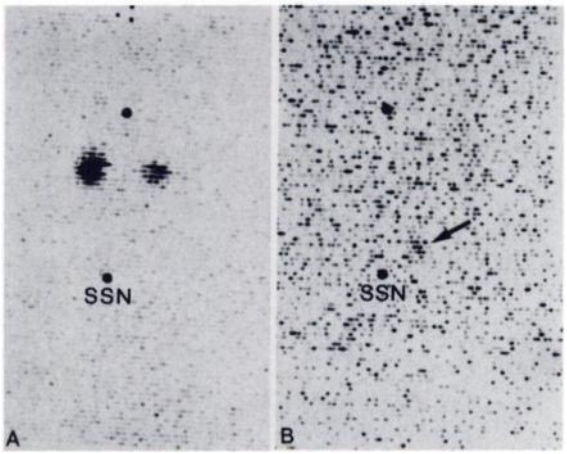

FIG. 3. A, B: I-131 images obtained on two patients with postoperative thyroid remnants. In both patients thyroglobulin levels were ≤20 ng/ml.

ported by Schneider, Schlumberger, and Ashcraft and their co-workers (*7,8,12*).

Several groups have reported abnormally elevated serum levels of thyroglobulin in patients with negative I-131 images (*5,8,12-14*). In the present study, two patients had elevated serum thyroglobulin levels despite repeatedly negative I-131 images. Routine determination of serum thyroglobulin may be of paramount importance in following the clinical course of such patients, since some investigators believe that serum thyroglobulin may be a more sensitive indicator of disease than the I-131 image (*12*).

It is apparent that the most important clinical application of the serum Tg assay is to monitor thyroid-cancer patients who are receiving thyroid hormone suppression therapy. If the assay can detect tumor activity reliably under such conditions, it will obviate the morbidity associated with the prolonged abstinence from replacement therapy required to perform I-131 imaging. However, to assure this degree of reliability, an assay with substantial sensitivity and specificity is required. On the basis of the present data, the assay used in this investigation appears to offer these attributes.

Based on this assay system, and considering thyroidectomized and I-131-ablated patients either on or off thyroid suppression therapy, we conclude that:

1. Serum thyroglobulin levels that are less than or equal to 20 ng/ml appear to indicate the absence of thyroid carcinoma.

2. Intermediate serum thyroglobulin levels between 20 and 60 ng/ml are observed in patients with postsurgical thyroid remnants and a small number of patients with active disease.

3. Serum thyroglobulin levels exceeding 60 ng/ml are indicative of active thyroid carcinoma, but may include some patients with latent disease without any clinical manifestations. Such patients require long-term follow-up.

FOOTNOTE

* Nuclear Medical Systems, Inc., Newport Beach, CA 92663.

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REFERENCES

1. KRISHNAMURTHY GT, BLAHD WH: Radioiodine I-131 therapy in the management of thyroid cancer. *Cancer* 40: 195-202, 1977
2. LO GERFO P, STILLMAN D, FEIND C: Serum thyroglobulin and recurrent thyroid cancer. *Lancet* 1:881-882, 1977
3. ECHENIQUE RL, KASI L, HAYNIE TP, et al: Critical evaluation of serum thyroglobulin levels and I-131 scans in post-therapy patients with differentiated thyroid carcinoma: Concise communication. *J Nucl Med* 23:235-240, 1982
4. VAN HERLE AJ, ULLER RP: Elevated serum thyroglobulin. A marker of metastases in differentiated thyroid carcinomas. *J Clin Invest* 56:272-277, 1975
5. BLACK EG, GIMLETTE TMD, MAISEY MN, et al: Serum thyroglobulin in thyroid cancer. *Lancet* 443-445, 1981
6. TANG FUI SCN, HOFFENBERG R, MAISEY MN, et al: Serum thyroglobulin concentrations and whole-body radioiodine scan in follow-up of differentiated thyroid cancer after thyroid ablation. *Br Med J* 2:298-300, 1979
7. PEZZINO V, COZZANI P, FILETTI S, et al: A radioimmunoassay for human thyroglobulin: Methodology and clinical applications. *Eur J Clin Invest* 7:503-508, 1977
8. SCHLUMBERGER M, CHARBORD P, FRAGU P, et al: Circulating thyroglobulin and thyroid hormones in patients with metastases of differentiated thyroid carcinoma: Relationship to serum thyrotropin levels. *J Clin Endocrin Metab* 51: 513-519, 1980
9. SCHNEIDER AB, LINE BR, GOLDMAN JM, et al: Sequential serum thyroglobulin determinations, ^{131}I scans, and ^{131}I uptakes after triiodothyronine withdrawal in patients with thyroid cancer. *J Clin Endocrin Metab* 53:1199-1206, 1981
10. LO GERFO P, COLACCHIO T, COLACCHIO D, et al: Thyroglobulin in benign and malignant thyroid disease. *JAMA* 241:923-926, 1979
11. BARSANO CP, SKOSEY C, DEGROOT LJ, REFETOFF S: Serum thyroglobulin in the management of patients with thyroid cancer. *Arch Intern Med* 142:763-767, 1982
12. ASHCRAFT MW, VAN HERLE AJ: The comparative value of serum thyroglobulin measurements and iodine 131 total body scans in the follow-up study of patients with treated differentiated thyroid cancer. *Am J Med* 71:806-814, 1981
13. COLACCHIO TA, LO GERFO P, COLACCHIO DA, et al: Radioiodine total body scan versus serum thyroglobulin levels in follow-up of patients with thyroid cancer. *Surgery* 91: 42-45, 1982
14. SCHLUMBERGER M, FRAGU P, PARMENTIER C, et al: Thyroglobulin assay in the follow-up of patients with differentiated thyroid carcinomas: comparison of its value in patients with or without normal residual tissue. *Acta Endocrinol* 98:215-221, 1981
15. GALLIGAN JP, WINSHIP J, VAN DOORN T, et al: A comparison of serum thyroglobulin measurements and whole body I-131 scanning in the management of treated differentiated thyroid carcinoma. *Aust NZ J Med* 12:248-254, 1982