Follow-up of Patients with Differentiated Thyroid Cancer Using Serum Thyroglobulin Measured by an Immunoradiometric Assay. Comparison With I-131 Total Body Scans

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An immunoradiometric assay for thyroglobulin (Tg), which allows quantification of Tg in the presence of anti-Tg, has been evaluated in patients with differentiated thyroid cancer. All patients had undergone thyroidectomy plus I-131 ablation. Three separate studies have been conducted.

1. Tg levels were compared with I-131 whole-body scans made at 48 hr in 22 patient studies. Both tests gave similar results in 19 of the studies, but in three patients the results of the tests were discordant.

2. Tg levels were compared with clinical status in 18 patients who were free of disease; 15 had Tg values <5 ng/ml, and three had measurable but normal Tg values. Three patients with metastatic disease had measurable Tg, and in two the values were above normal.

3. Sequential Tg measurements were made at intervals of 3 mo in 19 patients on thyroxine. Fifteen of these patients had identical results on two or more occasions.

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Thyroglobulin (Tg) is a thyroid-specific glycoprotein with molecular weight of ~660,000, which functions primarily as a carrier in thyroid-hormone synthesis. A minute portion of the total Tg stored in the gland is continuously released into the circulation and can be detected by radioimmunoassay (RIA) in the majority of normal individuals. The finding of an elevated Tg level is of no diagnostic specificity because it is found in Graves' disease, Hashimoto's thyroiditis, and benign and malignant nodules (*1,2*). In addition, it has not helped to define the presence of malignancy in patients who have had neck irradiation (*3,4*). Patients who have had total thyroidectomy for differentiated thyroid carcinoma should have no circulating Tg unless metastases are present, and in this setting Tg measurements have been a valuable tumor marker (*5,6*).

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This paper discusses (a) a comparison of serum Tg concentrations with whole-body I-131 scans in 22 studies; (b) a comparison of Tg concentrations and clinical status in a different group of 21 patients taking thyroxine; and (c) the results of serial Tg measurements in 19 patients taking thyroxine.

Conventional, double-antibody RIAs for Tg are restricted to sera that do not contain antithyroglobulin (anti-Tg) antibodies. Since (30 ± 10)% of patients with differentiated thyroid cancer have anti-Tg antibodies, we used a solid-phase, sandwich-type immunoradiometric assay for Tg, which allows a semiquantitative determination of Tg in the presence of anti-Tg (*7*).

MATERIAL AND METHODS

Patients studied. *Group A.* Seventeen patients (nine female, eight male) were studied, all undergoing total-body I-131 scans for detection of residual thyroid tissue or thyroid metastases. The age range was 14–59 yr (mean 37). Five patients had two scans giving a total of

22 patient studies. All patients had undergone total thyroidectomy for papillary or follicular thyroid carcinoma, or a lesser surgical procedure followed by ablation with I-131. They all gave written informed consent to have blood taken for measurement of Tg. Each patient stopped exogenous thyroxine for a minimum of 4 wk before scanning. At that time blood was drawn for measurement of TSH, Tg, and anti-Tg antibodies, and a 2 mCi dose of I-131 was then given orally. After 48 hr, anterior and posterior whole-body images, plus spot views of the neck, were made using a gamma camera with medium-energy collimator. Uptake of I-131 was measured using a probe detector over abnormal sites, or if none were found, over the thyroid region. Uptake measurements of 0.3% or less have been considered negative.

Group B. We studied 21 patients (15 female, six male) with differentiated thyroid cancer who had previously been treated by surgery or combined surgery and I-131 therapy and who were on thyroxine. Eighteen in this group were clinically free of disease and had negative whole-body scans in the past; three had clinical evidence of metastatic disease. None in this group had I-131 scans during the study.

Group C. Serial measurements of Tg were made at intervals of 3–4 mo in 19 patients who were without clinical evidence of disease and were taking thyroxine. Nine patients had two Tg measurements, six had three measurements, and four had four separate studies.

Radioimmunoassays of serum Tg, anti-Tg antibodies, and TSH. Serum Tg was measured by a solid-phase, sandwich-type, immunoradiometric assay (*7*). Thyroglobulin in the sample was bound to plastic cups coated with rabbit anti-Tg and then quantitated by its binding of rabbit I-125 anti-Tg. The normal range of Tg for individuals with intact thyroids is <40 ng/ml. In sera positive for anti-Tg, Tg concentrations were corrected by adding known quantities of Tg and determining the percentage that could be recovered. With the knowledge of how much native Tg had been measured originally, proportional corrections were made to obtain semiquantitative information on the actual serum Tg concentration. Recovery studies were carried out in all anti-Tg-positive sera with Tg values of 5–40 ng/ml. Levels of Tg <5 ng/ml are considered negative, and >40 ng/ml positive, regardless of the presence of anti-Tg antibodies.

Serum anti-Tg antibodies were measured as described previously (*8*). Serum TSH was determined by a modification of the method of Pekary et al. (*9*), normal values being <10 μU/ml.

RESULTS

Fifteen of 38 patients studied (39%) had anti-Tg antibodies.

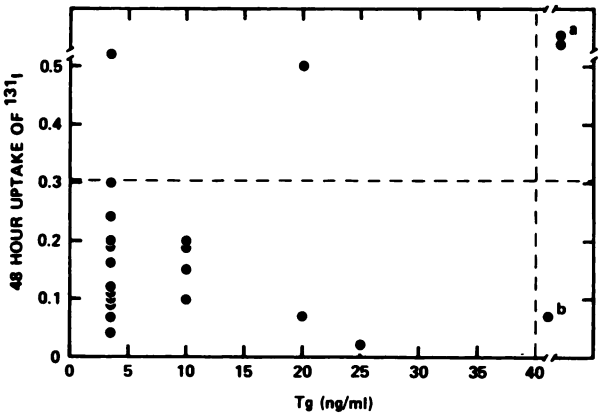

FIG. 1. Comparison of Tg level with 48-hr uptake of I-131 in 22 patient studies. Dotted lines show upper limits of normal for both studies. (a) Patient with elevated Tg off thyroid but normal Tg on thyroid. (b) Patient who received scanning dose of I-131 before blood was drawn for Tg measurement.

Group A. Comparison of serum Tg levels with 48-hr uptake of I-131 is shown in Fig. 1. Serum TSH at the time of Tg measurement was high in all patients: mean, 119 μU/ml; range, 79–>200 μU/ml. Nineteen of the 22 studies were in agreement provided the normal range for serum Tg, <40 ng/ml, applies to athyreotic patients, and a 48-hr I-131 uptake of ≤0.3% in the thyroid bed is considered normal. Seventeen patients had negative–negative correlations and two positive–positive correlations. The group of negative–negative correlations included 11 patients with Tg levels of <5 ng/ml, but in six studies small quantities of circulating Tg were detected. In the group with abnormal Tg results and positive scans, one patient ("a" in Fig. 1) had an elevated Tg only while off thyroxine. She also had scan evidence of lymph-node metastases.

Of the three patients who had disparate results, one patient ("b" in Fig. 1) had a Tg value of 45 ng/ml but no uptake of I-131. In this case blood was drawn for Tg measurement 48 hr after administration of the 2 mCi scanning dose. Interference of I-131 in the Tg assay was excluded as the cause of this finding. This departure from the protocol occurred only in this patient, and a subsequent Tg of <5 ng/ml and benign clinical course suggested that it was a false-positive result. The other two patients had normal Tg values but abnormal scans. In these two, Tg levels were <5 and 20 ng/ml, with uptakes of 0.9 and 0.5%, respectively, in the area of the thyroid bed.

Group B. Figure 2 shows Tg results in 21 patients taking thyroid for suppressive therapy. Eighteen patients had no clinical evidence of disease and 15 had Tg levels of <5 ng/ml, whereas three patients had detectable Tg values. Of three patients with proven metastatic disease, two had Tg values clearly above normal, but the third had a Tg concentration of 20 ng/ml. This last patient has an unusual cancer, with widespread bony metastases

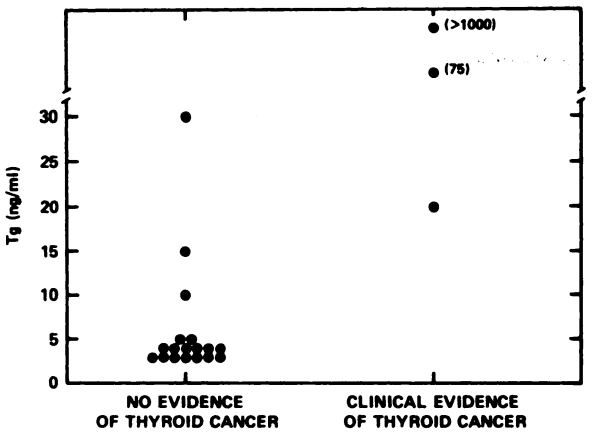

FIG. 2. Tg values in 18 patients with no evidence of thyroid cancer, and in three with known metastases.

(biopsy proven) that do not accumulate iodine and apparently produce little Tg.

Group C. Six of nine cases with two Tg measurements had identical results of <5 ng/ml. In the remaining three cases the Tg results were similar: 10 against 5 ng/ml, 5 against 15 ng/ml, and 30 against 25 ng/ml. All six patients who had three measurements had identical Tg values of <5 ng/ml. Three of four patients with four measurements had levels of <5 ng/ml, whereas one patient had three Tg values of <5 ng/ml with the fourth at 20 ng/ml.

DISCUSSION

In three respects differentiated thyroid cancer is unlike most other human cancers. First, it is associated with an excellent prognosis, especially in patients less than 40 yr old who have no evidence of distant metastases (*10,11*). Second, by using I-131 whole-body scans it is possible to detect (and treat) local and distant metastases before they are found by other methods (*12*). Third, in patients who have had total thyroidectomy, thyroglobulin measurements can be used as another indicator of residual or metastatic cancer (*5,13*).

The main purpose of this study was to compare the diagnostic value of Tg measurements, by a new immunoradiometric assay, with the whole-body I-131 scan. If both investigations always provided identical outcomes, measurement of Tg could replace some scans, which have logistic and radiation problems. In the course of the study, several important facts became apparent. First of all, it is essential to define the normal values for each test. If there is ablation of the thyroid there should be zero I-131 uptake, but in clinical practice this is virtually impossible to achieve, and an uptake of 0.3% or less in the region of the thyroid bed is probably of no consequence. Therefore, this value was accepted empirically as normal. However, one should bear in mind that a positive scan of >0.3% is not synonymous with metastases since it could be due to a remnant of normal thyroid.

After total thyroidectomy, Tg levels are expected to fall below the limit of detectability unless residual or recurrent functioning cancer is present. However, radioiodine ablation therapy can cause long-term slow release of Tg from a tiny residuum of cells in the absence of any other evidence of persisting disease (*14*). Therefore, in order to avoid false-positive results, we set the normal range of Tg for athyreotic individuals at <40 ng/ml (identical to that in normal controls with intact thyroids).

There was a good correlation between negative scans and unmeasurable (<5 ng/ml) Tg results. Only one of 12 patients with Tg <5 ng/ml had a positive scan, which was most likely due to residual normal thyroid. Seven patients had measurable Tg concentrations (10–45 ng/ml) but extremely low I-131 uptake. Fui et al. (*6*) found that seven of 21 patients with measurable Tg up to 50 ng/ml had normal scans, but 14 had abnormal scans. They did not define the degree of abnormality on scan.

There is some controversy about what dose of I-131 should be used for scanning. Some report that 10 mCi, or even 30 mCi, are superior to 2 mCi, and it might be argued that small lesions secreting Tg would have been detected with larger scanning doses. Against this is the fact that whole-body anterior and posterior images were obtained by camera (not scanner), and no form of background subtraction was used, making it unlikely that metastases were missed in these patients. A more probable explanation for the presence of Tg is that these patients had received I-131 therapy in the past year and that Tg was still leaking from damaged tissue, rather than from a viable cancer. This explanation is supported by the fact that followup Tg measurements in three of these patients gave the same or declining results.

In the one patient with no uptake of I-131 but Tg of 45 ng/ml, the discrepancy may have been due to the scanning dose of I-131, which could have released Tg from a tiny residuum of cells (*14*). It was not due to I-131 interference with the assay. It is important, therefore, to obtain the serum for Tg measurements before administration of I-131 for either scanning or therapy. Conversely, one patient with a normal Tg value of 20 ng/ml had an abnormal scan, indicating that a single Tg value in the defined normal range has a relatively low predictive value for absence or presence of disease unless previous Tg levels are available for comparison.

Of considerable concern was the patient who had a normal Tg while she was taking thyroxine but an elevated Tg off thyroxine. On scan she showed abnormal uptake of I-131 in lymph nodes. It might be argued that her cancer was adequately treated by thyroid medication, since Tg was suppressed, but the counterargument is that to detect metastases on scan the patient must be

off thyroxine.

In those patients (Group B) who were taking thyroxine and had no evidence of cancer, three had measurable Tg concentrations. Possibly these patients should have whole-body I-131 scans, but since previous scans showed no abnormality and the patients have been under long-term evaluation with no clinical evidence of disease, this does not seem warranted. All three patients with proven metastases had measurable Tg, but in one patient the value was within the normal range.

There is no unified method of resolving all these data. After total thyroidectomy the most appropriate approach is to do a whole-body scan with the patient off T_4 for at least 4 wk, or off T_3 for 2 wk (*15,16*). If the scan shows an uptake of >0.3%, I-131 therapy would be prescribed to ablate residual thyroid tissue. Once there is no evidence of abnormality on scan, a Tg "baseline" value should be determined, and then serial Tg measurements can be used to follow the patient. A rise in Tg should be an indication to repeat the whole-body scan.

We conclude that serum Tg measurements can be useful in the follow-up of patients with thyroid carcinoma, but Tg results have to be interpreted in context with the patient's history and, if possible, with preceding Tg results for comparison.

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