Therapeutic Doses of Iodine-131 Reveal Undiagnosed Metastases in Thyroid Cancer Patients with Detectable Serum Thyroglobulin Levels

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Serum thyroglobulin (Tg) measurements in patients with treated differentiated thyroid cancer are usually well correlated with the presence or absence of residual or metastatic thyroid tissue. However, it is not rare to find a patient with detectable serum Tg levels but negative ^{131}I whole-body scan (WBS) and no evidence of disease activity. To clarify the reason for this discrepancy, we decided to perform the WBS after the administration of a therapeutic dose of ^{131}I in 17 consecutive patients in whom serum Tg was detectable while the WBS performed with a 5 mCi tracer dose was negative (12.6% of 135 patients studied with both WBS and serum Tg). The result of this study demonstrated that after this procedure the WBS became positive for significant residual or metastatic areas of radioiodine uptake in all patients but one. Such data indicate that in our patients the presence of circulating Tg is not a false-positive Tg result, but is due to the presence of residual or metastatic tissue that is not detected in the conventional WBS, that can be visualized using therapeutic doses. Preliminary follow-up data indicate that this procedure may also have therapeutic effect, although the relevance of this aspect remains to be established.

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Serum thyroglobulin (Tg) measurements are usefully employed in the management of patients with differentiated, papillary and follicular, thyroid cancer (*1–5*). After total thyroidectomy the presence of detectable serum Tg concentration is an index of residual or metastatic thyroid tissue and is usually well correlated with positive iodine-131 (^{131}I) whole-body scan (WBS) (*6–11*). Furthermore, elevated serum Tg levels are present also in the case of nonfunctioning metastases, that are not detected by WBS, but are diagnosed by other clinical or radiologic methods (*8,11*). However, in some cases it is possible to find detectable serum Tg levels in patients with no evidence of residual or metastatic thyroid tissue by both WBS and other techniques. The explanation offered for these apparently false-positive Tg results are either an interference of anti-Tg autoantibodies (*12*) in the Tg assay or a low sensitivity of the WBS in detecting small residues or metastases (*13–15*).

To verify this last possibility we decided to treat our patients with apparently false-positive serum Tg results and negative WBS, with a therapeutic ^{131}I dose and to repeat the WBS after this procedure.

PATIENTS AND METHODS

Patients

Seventeen patients (12 females and five males, ranging in age between 16 and 69 yr) were selected for this study. They had been previously treated with total thyroidectomy for differentiated thyroid cancer (papillary in 16 and follicular in one) followed by therapy with ^{131}I (50–150 mCi) for ablation of their thyroid residue. After this treatment they all were apparently free of disease except that their serum Tg was found to be detectable, and in some cases elevated, ranging between 15 and 976 ng/ml with negative tests for anti-Tg autoantibodies and negative WBS performed with a tracer dose of 5 mCi of ^{131}I. An extensive evaluation of these patients did not show any clinical or radiologic evidence of disease

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activity, although diffuse lung uptake had been previously found in four patients. The possible ingestion of iodine before performing WBS was ruled out by history and by determination of urinary iodine excretion. The possibility that negativity of WBS could be due to an inadequate withdrawal of thyroid suppressive therapy was ruled out by the finding of high serum TSH concentrations in all patients.

After the conventional WBS performed with 5 mCi tracer dose, a therapeutic ^{131}I dose (75–140 mCi) was administered to each patient and the WBS was repeated after 5–10 days. These 17 cases represented 12.6% of 135 consecutive patients undergoing 5 mCi WBS and serum Tg measurement. Follow-up data were available in 12 patients, and consisted in serum Tg measurement and WBS at time intervals of 8–12 mo from the first study and treatment.

Scanning Procedure

Total-body scan was performed using a rectilinear scanner.* In all cases the conventional WBS was performed 48–72 hr after a tracer dose of 5 mCi ^{131}I. The time of scan was correlated with the activity (CPS), and ranged between 50 and 150 min. Scan speed was 50 cm/min for ≤200 cps and 100 cm/min for 200–500 cps. For more than 500 cps the scan speed was 200 cm/min. WBS after therapeutic doses of ^{131}I (75–140 mCi) was performed 5–10 days after the administration of the dose.

Measurement of Serum Tg

Serum Tg was measured using a specific immunoradiometric assay (IRMA) as reported in details (*16*). Briefly, 200 μl of unknown or standard were pipetted in plastic polystyrene tubes coated with rabbit anti-Tg antiserum. After 18 hr incubation at room temperature, tubes were washed three times and then 200 μl of ^{125}I-labeled anti-Tg antibody (3,500–4,000 dps) were added to each tube. After 24 hr incubation at room temperature the mixture was removed, the tubes were washed and counted. Results were expressed as percent of ^{125}I anti-Tg antibody bound to the tubes and plotted against the Tg concentrations used for the standard curve. The results of serum Tg measurement using this IRMA method are very well correlated with the results obtained with conventional RIA methods (*16*). Its sensitivity is 3 ng/ml and the intra-assay coefficient of variation is 6% and inter-assay is 11%. Serum Tg values in our laboratory range from <3 to 30 ng/ml (mean ± s.d. 12 ± 11 ng/ml) in normal adult subjects. Since circulating anti-thyroglobulin antibodies (TgAb) interfere in our Tg assay producing false-negative results, we routinely screen all patients for serum TgAb using the passive haemagglutination technique. No patient in this study had positive TgAb titers.

RESULTS

As shown in Table 1, basal WBS performed with 5 mCi tracer dose was negative in all patients while serum Tg was detectable in a range of 15–976 ng/ml. After the administration of the therapeutic dose of ^{131}I (75–

TABLE 1

	First study				Second study*			
Patient no.	Tg ng/ml	5 mCi WBS	^{131}I mCi	Postdose WBS	Tg ng/ml	5 mCi WBS	^{131}I mCi	Postdose WBS
1	15	Neg	80	Residue		Neg		
2	21	Neg	100	Negative	26	Neg		
3	46	Neg	100	Lung Mediastinal nodes	50 (22)†	Lung±	100	Lung
4	153	Neg	90	Lung	84	Neg	100	Negative
5	443	Neg	127	Lung	104 (35)	Neg	100	Negative
6	78	Neg	75	Lung Mediastinal nodes				
7	412	Neg	100	Lung + nodes				
8	53	Neg	100	Residue	51	Neg		
9	61	Neg	111	Mediastinal nodes	48 (28)	Neg		
10	976	Neg	137	Residue, lung, nodes	425	Neg		
11	240	Neg	127	Residue Mediastinal nodes	390	Residue	100	Lung Mediastinal nodes
12	131	Neg	92	Residue Mediastinal nodes	125	Mediastinal nodes	120	Mediastinal nodes
13	22	Neg	95	Residue Mediastinal nodes				
14	60	Neg	127	Residue	52	Neg		
15	51	Neg	140	Lung				
16	120	Neg	80	Lung	80 (10)	Neg	134	Lung
17	72	Neg	112	Lung				

*Second study was performed 8–12 mo after the first study and treatment.

†(n): Number in parenthesis refers to the result of serum Tg for patients who had a third study, 8–12 mo after the second study.

140 mCi) WBS was still negative only in one patient. In the other 16 patients areas of radioiodine uptake were present in the thyroid bed in three cases, in the lung in five cases, in the mediastinum in one case, in the lung and mediastinum in two cases, in the thyroid bed and the mediastinum in three cases, in the mediastinum and cervical nodes in one case and in the thyroid bed plus cervical nodes plus lung in one case.

Follow-up data are presently available in 12 out of 17 patients and include one or two further WBS and serum Tg measurement (second and third study) performed at time intervals of 8–12 mo. As shown in Figure 1, at the last follow-up serum Tg was significantly reduced in seven cases, increased in one and unchanged in the others. Results of the second WBS are reported in Table 1: the 5 mCi WBS was again negative in nine patients in spite of positive serum Tg assays. Three patients were submitted to a second therapeutic ^{131}I dose and one of them showed positive post-treatment WBS with clear-cut radioiodine lung uptake. Positive basal WBS were observed in the remaining three patients with ^{131}I uptake in the lungs in one case, in the mediastinal nodes in one and in the thyroid bed in one. Positive post-treatment scans were obtained in each of these three patients and showed activity in the metastatic areas already detected by the basal scan in two and in the lung and mediastinal areas in the patient showing only a thyroid residue in the basal scan.

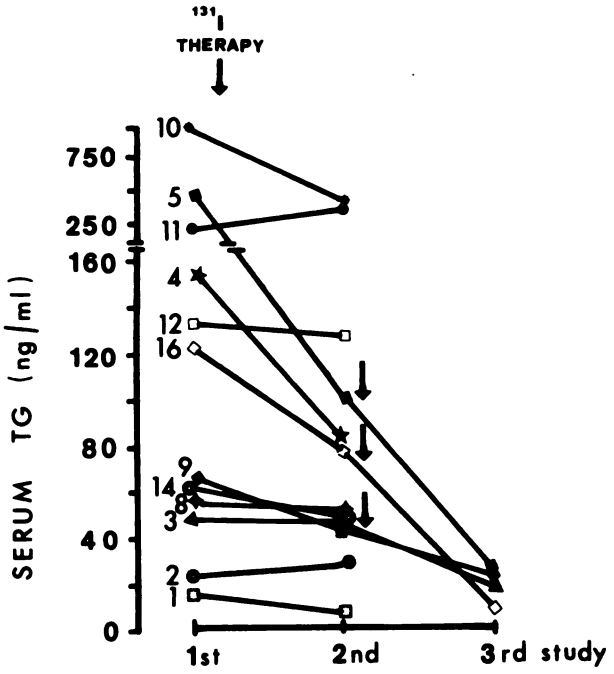

FIGURE 1
Changes in serum Tg after therapeutic doses of radioiodine in patients with negative basal WBS. Arrows indicate the administration of therapeutic ^{131}I doses; patient number is indicated near each symbol.

DISCUSSION

This study was undertaken to clarify the problem of patients with detectable serum Tg levels after total thyroidectomy for differentiated thyroid cancer with no clinical, radiologic, or scintigraphic evidence of residual or metastatic thyroid tissue. This event accounted for 12.6% of our patients submitted to routine 5 mCi WBS. We afforded this issue by performing WBS after the administration of therapeutic doses of ^{131}I, in order to increase the sensitivity of the scintigram, as indicated in previous studies (*11,13–15*).

This procedure turned out to be effective in revealing undiagnosed metastases in 13 patients and thyroid residues in three patients. Similar results have been reported in two patients by Galligan et al. (*11*) and in 18 patients by Schlumberger et al. (*17*). In the present series, only one patient (with basal Tg levels of 26 ng/ml) had postdose WBS still negative for radioiodine uptake and we have no explanation for the circulating Tg in this case, although the presence of thyroid tissue retaining the ability to produce thyroglobulin but loosing the ability to take up iodine has been reported (*18*).

Admittedly the use of new generation Anger cameras may prove to be advantageous and may result in a reduced number of negative basal 5 mCi WBS. As pointed out by Ramanna et al. (*19*) such devices may well prove to be more sensitive than rectilinear scan in detecting low radioiodine-avid tissue, when tracer ^{131}I doses of 10 mCi are used. However, Galligan et al. (*11*) and more recently Schlumberger et al. (*17*) demonstrated that, even using an Anger camera, there are still some patients with high serum Tg whose metastases are not detected by 2 mCi scan and are discovered only using 100 mCi doses.

Our results indicate that detectable serum Tg levels are almost always indicators of the presence of residual or metastatic thyroid tissue also in the case of patients with no other evidence of disease activity. These metastases are missed by conventional WBS, but can be diagnosed by WBS performed after administration of high radioiodine doses. The question of whether this procedure has also therapeutic effect remain to be established. Follow-up data, including WBS and serum Tg measurement were available in 12 of our 17 patients submitted to therapeutic doses of ^{131}I. Indirect evidence of at least some therapeutic effect was obtained in seven patients who showed a reduction of serum Tg with or without a reduced ^{131}I uptake at the scan. In keeping with our data are the results reported by Schlumberger et al. (*17*) during the preparation of the present manuscript. These authors showed normalization of x-ray findings after therapeutic ^{131}I doses in patients who had positive serum Tg measurements, negative basal WBS in the presence of radiologically proven lung metastases. In view of these demonstrations we feel that this approach may be considered in selected patients, i.e., those

who show consistently positive Tg test on repeated observations. This approach is particularly indicated in the patients who have evidence of metastatic disease but negative scans with current diagnostic doses.

NOTE

* Ital Elettronica S.p.A., Rome, Italy.

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