Paradoxical Changes in Iodine-131 Scintigraphic Findings in Advanced Follicular Thyroid Cancer

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We present the findings on iodine-131 (^{131}I) scintigraphy, thallium-201 (^{201}Tl) scintigraphy and quantitative thyroglobulin (QTG) estimation in two patients with follicular carcinoma of the thyroid with extensive metastases. The lesions were initially seen on ^{131}I scintigraphs, but were not subsequently visualized with scanning doses of ^{131}I (5 mCi), while retaining their ability to produce increasing amounts of thyroglobulin and take up ^{201}Tl. Implications in choosing the appropriate diagnostic tests in the management of differentiated thyroid cancer are discussed.

J Nucl Med 1993; 34:1574–1576

The three diagnostic modalities that have been found to be most useful in the detection of recurrent or metastatic differentiated thyroid cancer include ^{131}I scintigraphy, ^{201}Tl scintigraphy and quantitation of serum thyroglobulin (QTG) (*1–10*). However, there is no consensus on which of the three tests should be used—either alone or in conjunction with the others—for the routine management of differentiated thyroid carcinoma after thyroidectomy (*1–10*). We present the changes in the findings of these three tests during disease progression in two patients with follicular thyroid cancer with extensive metastases.

METHODS

All studies were performed when the patients were off thyroid suppression with serum TSH levels of at least 50 mU/ml. Doses of both ^{131}I and ^{201}Tl (5 mCi) were used for the studies. The Searle Radiographic 75000 series, Model 6413 PHO/Gamma LFOV scintillation camera system (Searle, Des Plaines, IL) was used to obtain the images. Serum thyroglobulin levels were measured using a double antibody radio-immunoassay (Kalibre High Sensitivity Thyroglobulin Radio-immunoassay, Smith Kline & Beecham, Van Nuys, CA). The reference range in this assay is 0–60 ng/ml.

Received Nov. 10, 1992; revision accepted Apr. 27, 1993.
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CASE REPORTS

Case One

A 72-yr-old male initially presented in 1985 with hemoptysis and was diagnosed with invasive follicular carcinoma of the thyroid involving the trachea. Treatment consisted of partial resection of the tumor and radiation therapy (5200 R) to the neck. QTG was 380 ng/ml. Subsequently, due to visualization of persistent tumor in the superior mediastinum as well as pulmonary metastases on ^{131}I scintigraphy, the patient received multiple doses of ^{131}I (667 mCi over the next 3.5 yr). In May 1990, both ^{131}I and ^{201}Tl scintigraphy were performed. Both studies showed multiple lesions in the lungs and left mediastinum (Figs. 1A and 1B).

These findings were confirmed radiologically. Serum TSH was 50 mU/ml and QTG was greater than 5000 ng/ml. The patient was administered an additional 166 mCi of ^{131}I. Fourteen months later, ^{131}I scintigrams showed minimal uptake of ^{131}I in the chest (Fig. 1C). Concomitant ^{201}Tl scintigraphy however revealed extensive metastatic spread with uptake in the chest, and right axillary areas (Fig. 1D). The findings were confirmed radiologically. Serum TSH was 71.3 mU/ml and QTG was greater than 5000 ng/ml.

Case Two

A 44-yr-old male presented with a history of persistent low back pain. A skeletal survey revealed a lytic lesion at T6. On computerized tomography (CT), a large subcarinal mass eroding into T6, multiple pulmonary nodules and a 2-cm mass in the thyroid gland were seen. The pulmonary nodule was biopsied and diagnosed to be metastatic medullary carcinoma of the thyroid on histopathological examination. The patient received radiation therapy (4000 R) to T6–T8 and the mediastinum, in addition to 3 cycles of VP-16 and cis-platinum. Four months later, ^{131}I follow-up scintigraphy was performed and revealed intense uptake in the intertrochanteric area of the right femur. This lesion was biopsied and found to be metastatic follicular thyroid carcinoma on histopathological examination (Fig. 2). Immunoperoxidase studies performed on the biopsied tissue were positive for thyroglobulin and negative for calcitonin. QTG was 470 ng/ml. Based on these findings, the diagnosis was changed to follicular carcinoma of the thyroid. During the next 18 mo, the patient received a cumulative dose of 750 mCi of ^{131}I. In May 1990, both ^{131}I and ^{201}Tl scintigraphy showed uptake in the lungs, abdomen and pelvis (Figs. 3A and 3B). These findings were confirmed on CT. Serum TSH was 75.2 mU/ml and QTG was greater than 5000 ng/ml. The patient received an additional dose of 216 mCi. Three months later, ^{131}I scintigraphy showed a focal area of uptake in the left thorax (Fig. 3C). Concomitant ^{201}Tl scintigraphy, however, showed uptake in the lungs, abdomen and pelvis (Fig. 3D).

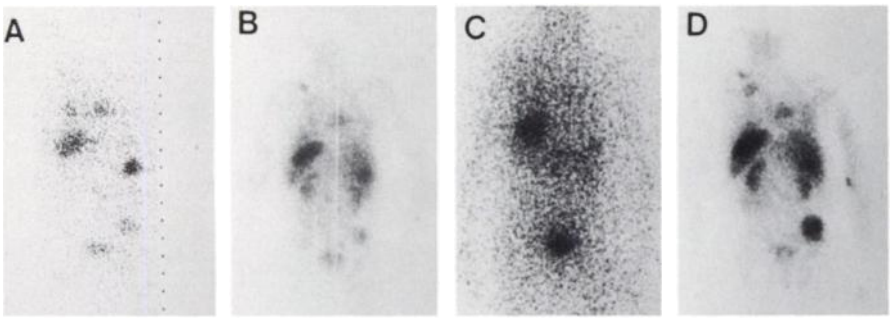

FIGURE 1. Case 1: Initial studies A & B: Iodine-131 whole-body scan (A) shows multiple abnormal areas of uptake in the left mediastinum and both lungs. Thallium-201 whole-body scan (B) shows a focus of abnormal uptake in the mediastinum. Subsequent studies C and D: Iodine-131 whole-body scan (C) shows mild diffuse uptake in the lungs. Thallium-201 whole-body scan (D) shows foci of abnormal uptake in the mediastinum and lungs.

These findings were confirmed radiologically. Serum TSH was 69 mU/ml and QTG was greater than 5000 ng/ml. The patient died 7 mo later due to progressive disease.

DISCUSSION

In these two patients with follicular carcinoma with extensive metastases, both ^{131}I and ^{201}Tl scintigrams initially were positive for all known metastatic lesions. Subsequent studies showed more intense uptake of ^{201}Tl. However, there was a progressive decrease in ^{131}I uptake by the metastatic lesions. In addition, new sites of metastatic involvement were visualized on ^{201}Tl scintigraphy, but not on scanning doses of ^{131}I (5 mCi). Post-therapy scans, however, did show ^{131}I uptake in most of the metastatic sites in both patients.

Most malignant lesions, even those of a differentiated thyroid cancer, are heterogenous with respect to cell differentiation. The uptake of ^{131}I in individual lesions may vary as a result of the blood flow, histology and the functional capacity of the tissue (*11,12*). There have been a few anecdotal reports in the literature of patients with thyroid cancer with widespread metastasis in whom the lesions lost their capacity to concentrate ^{131}I during the course of the disease (*13,14*). The proposed explanation has been dedifferentiation of the tumor, either de novo or due to external beam radiation therapy. Leeper noted that in some patients with papillary carcinoma and bony metastases who had radiation therapy, a radioiodine resistant anaplastic conversion occurred. He suggested that the radiation therapy may have caused transformation of more benign cells to extremely anaplastic cells (*13*). Samaan et al. found that four patients with papillary thyroid cancer with pulmonary metastases had uptake of radioactive iodine initially, but with disease progression, and had little or no uptake of radioiodine. On biopsy, these lesions were found to have undergone anaplastic changes, presumably de novo as three of the four patients did not receive ^{131}I therapy (*14*). In the two patients described in this report, neither patient received external beam radiation therapy, but they both received therapeutic doses of ^{131}I therapy during the period between the two sets of studies shown here when the lesions lost their capacity to take up ^{131}I.

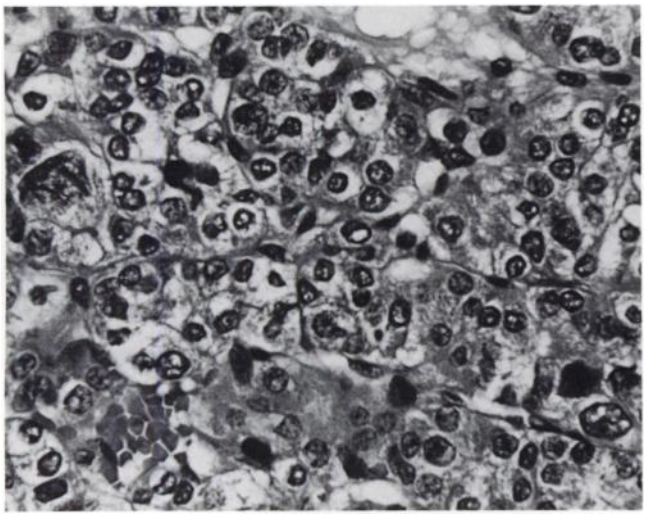

FIGURE 2. Follicular carcinoma of the thyroid metastatic to the hip (Case 2). The tumor forms small follicles separated by a fine fibrovascular stroma. There is nuclear atypia and pleomorphism of the follicular cells (40×).

We hypothesize that instead of the lesions having undergone an anaplastic change, the therapeutic doses of ^{131}I may have preferentially destroyed subpopulations of thyroid cancer cells that had the functional capacity to accumulate ^{131}I in the heterogenous tumor mass.

Alternatively, the lesions may have been "stunned" and could have temporarily lost the capacity to concentrate iodine, as a result of radiation damage. This phenomenon has been reported with both scanning doses (*15,16*) and therapeutic doses of ^{131}I (*17,18*) and can pose a considerable dilemma in the management of these tumors.

Serum thyroglobulin levels were initially elevated in both patients, and continued to rise as the disease progressed. Usually, the capacity of the tumor to secrete thyroglobulin does appear to indicate that it will concentrate iodine although the relationship between these two cellular functions varies considerably from one tumor to another (*19*). However, as seen in these two patients, synthesis and secretion of thyroglobulin by tumor cells is a process independent of the iodine uptake capacity of these cells and appears to be largely independent of TSH control (i.e., the tissue has functional autonomy). Hence, retention of thyroglobulin secreting activity by the tumor cell does not necessarily mean that it will concentrate iodine as well.

Thallium-201 is taken up in various tumors through several cellular transport systems (*20–22*). The amount of ^{201}Tl taken up by a tumor is influenced by factors such as bloodflow, viability, cell membrane permeability and tu-

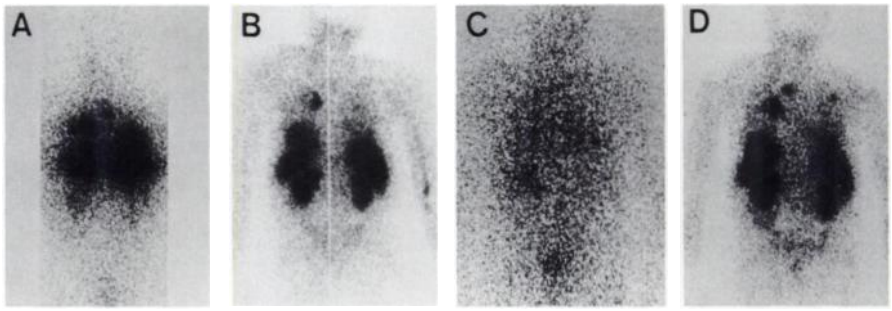

FIGURE 3. Case 2: Initial studies A & B: Iodine-131 whole-body scan (A) shows multiple abnormal areas of uptake in the lungs, abdomen and right hip. Thallium-201 whole-body scan (B) shows foci of abnormal uptake in the chest, abdomen and right hip. Subsequent studies C and D: Iodine-131 whole-body scan (C) shows mild diffuse uptake in the chest and abdomen with a focus of uptake in the left upper quadrant of the abdomen. Thallium-201 whole-body scan (D) shows foci of abnormal uptake in the chest, abdomen and right hip.

mor type (*23*). The role of ^{201}Tl scintigraphy in these two cases is noteworthy as the scan findings correlated well with the observed progression of disease in both patients.

The findings in these two cases help demonstrate that each of these three diagnostic modalities evaluates a different cellular function of the thyroid cancer cell and that they cannot be interchanged. Rather, use of the three modalities should be tailored as the situation warrants in each patient.

ACKNOWLEDGMENT

The authors thank Dr. Virginia LiVolsi, MD, Department of Pathology, University of Pennsylvania, for her review of pathology slides and Edward Yeager and Zsuzsanna Ezra for preparing illustrations.

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