Metastatic Follicular Carcinoma of the Thyroid: Reappearance of Radioiodine Uptake

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Dedifferentiation of well-differentiated thyroid carcinoma is a well-known phenomenon that may lead to the disappearance of radioiodine uptake in tumors and the inability to treat patients with radioiodine. We report a patient in whom the ^{131}I uptake progressively diminished to such low levels after a cumulative dose of 31.5 GBq that further ^{131}I administration was considered nonbeneficial. Thereafter, metastases in the lungs and skeleton progressed. Because of the absence of any other therapeutic options, nearly 2 yr later we decided to reperform ^{131}I measurements and scanning under hypothyroid conditions. All known metastatic lesions this time showed intense ^{131}I uptake, more than 10-fold the previously measured values. High-dose ^{131}I treatment was restarted.

Key Words: thyroid carcinoma; metastasis; radioiodine therapy

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Metastatic thyroid carcinoma is one of the major indications for diagnostic studies and subsequent treatment with radioiodine (*1*). When metastatic lesions show sufficient radioiodine uptake, treatment with such radiopharmaceutical has been shown to significantly prolong life and in a number of patients to even achieve a cure (*2,3*). However, in the course of multiple-dose treatment regimens, selection of noniodine accumulating tumor cells and/or cellular dedifferentiation may cause a decline of iodine uptake in tumor cells resulting in a detriment of radioiodine treatment effectiveness (*2*). This may result in such low uptake values that effective treatment is no longer possible (*2*). We report a patient in whom ^{131}I treatment for metastatic follicular thyroid carcinoma was discontinued for this reason. However, in the course of her disease, progressive metastases without any other therapeutic option made us decide to re-evaluate radioiodine uptake of the metastatic tumors.

CASE REPORT

A 64-yr-old female presented with a growing nodule in a pre-existing multinodular goiter which had been visualized as a cold area of the thyroid on a [^{99m}Tc]pertechnetate scan. Cytological examination of fine-needle aspirate did not rule out malignancy. Therefore, partial and subsequent total thyroidectomies were performed. Histological examination showed follicular adenocarcinoma of the thyroid invading blood vessels and surrounding tissue. The patient was kept off thyreomimetic medication for 1 mo to achieve high thyroid-stimulating hormone (TSH) levels.

The patient was then given an i.v. injection of 37 MBq sodium ^{131}I. Radioiodine distribution and retention was evaluated 2 and 7 days after injection using a shadow-shield, whole-body counter and gamma camera imaging equipped with a high-energy, parallel-hole collimator. The ^{131}I study revealed a large area of ^{131}I uptake in the neck. Because of these findings, the patient was treated with 5.5 GBq ^{131}I. Scintigraphic images obtained after the therapeutic dose revealed two pulmonary metastases along with the known thyroid remnants in the neck. Thyreomimetic treatment was started at a dosage to ensure suppressed TSH levels. Five, 10 and 15 mo after thyroidectomy, the patient was re-evaluated after temporary discontinuation of thyreomimetic medication to ensure elevated TSH levels. These studies showed progressive tumor growth in the neck and cervical spine and progressive metastases in the chest. Since sufficient ^{131}I uptake for a partial therapeutic effect was noted, treatment was continued with 5.5, 5.5 and 7.5 GBq, respectively (Table 1) for several months. Over time, ^{131}I uptake in the lesions progressively diminished.

Whole-body imaging after i.v. injection of 75 MBq ^{201}Tl-chloride [to assess noniodine-accumulating tumor (*4*)] consistently showed uptake in the neck and lungs. Rapid growth of the tumor in the neck necessitated surgical debulking of the tumor 16 mo after thyroidectomy. Complete resection was impossible since the trachea and recurrent nerves were encapsulated by the tumor. Twenty months after thyroidectomy, there was still ^{131}I uptake in the neck and lungs. A new lesion in the left femur was visualized. The patient was again treated with 7.5 GBq ^{131}I. The thyroglobulin level, a serum marker for differentiated thyroid carcinoma (*5*), was now measurable due to the disappearance of auto-antibodies against thyroglobulin, which was clearly elevated (200 pmole/liter, normal value <10 pmole/liter). Evaluation 5 mo later (25 mo post-thyroidectomy) showed only minimal ^{131}I retention in the large neck tumor.

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TABLE 1
Radioiodine Examinations under Hypothyroid Conditions, Laboratory Findings, Subsequent Therapeutic ^{131}I Dose and Scintigraphic Findings

Month*	Day p.i.	WBR† (%)	Uptake (%) Neck	Uptake (%) Chest	TSH‡ (mE/l)	TG§ (pmole)	I¶ (μmole)	Therapeutic dose (GBq)	^{131}I scintigraphy
1	0	100	5.2	n.e.**	39.0	a.a.	0.15	5.5	Activity in neck (7 × 4 cm) and two spots in lungs
	2	16.3	9.5						
	7	8.8	3.7						
5	0	100	4.2		31.6	a.a.	0.05	5.5	Activity in neck and multiple spots in lungs (progression)
	2	9.5	2.9	<0.5					
	7	2.5	0.7	<0.1					
10	0	100	3.3		32.1	a.a.	0.03	5.5	Activity in neck and multiple spots in lungs (strong progression)
	2	3.4	0.6	<0.5					
	7	1.0	0.2	<0.1					
15	0	100	3.3		23.4	a.a.	0.08	7.5	Activity in neck and several spots in lungs (regression of pulmonary lesions)
	2	4.5	0.7	<0.5					
	7	0.7	0.1	<0.1					
20	0	100	2.9		31.5	200	0.05	7.5	Vague activity in neck and several spots in lungs (stable); new lesion left femur
	2	2.8	0.4	<0.5					
	7	0.5	0.1	<0.1					
25	0	100	2.0		33.5	194	0.02	none	Vague activity in neck; no visualization of metastases in skeleton and lungs.
	2	5.4	0.5	<0.5					
	7	1.5	0.1	<0.1					
45	0	100	4.5		32.0	209	0.03	7.5	Increased activity in neck, both lungs and skeleton (spine, both femora, orbita, both humeri)
	2	52.0	4.2	18.9					
	7	24.7	2.6	8.9					

*Months after total thyroidectomy.
†Whole-body retention.
‡Thyroid stimulating hormone (normal values 0.4–4.0 mE/l).
§Thyroglobulin normal value off thyreomimetics <10 pmole/liter); a.a. = not evaluable due to too high auto-antibody levels against thyroglobulin.
¶Total plasma iodine level (normal values in hypothyroid phase <0.15 μmole/liter; in case of excess iodine intake, such as after injection of radiographic contrast agents higher than 1 μmole/liter). Measurements according to the method reported by Foss et al. (*9*).
**n.e. = not evaluable due to high uptake in the neck.

Thyroglobulin remained at the same high level. Iodine contamination as the cause for low ^{131}I uptake was excluded (Table 1). Thallium-201 scanning also revealed uptake in left supraclavicular lymph nodes and stable, diffuse pulmonary uptake. The lack of sufficient iodine uptake resulted in discontinuing ^{131}I treatment.

External beam irradiation on the neck and cervical spine (27 × 2 Gy, 6 to 10 MeV photons) augmented with a weekly low dose adriamycin infusion 10 mg/m^2 for 6 wk) resulted in a stable local condition and amelioration of the radicular syndrome of the left arm. In the following year, the patient was repeatedly admitted for complications of newly developed skeletal metastases, such as fractures of both femora (osteosynthesis and single dose external beam irradiation (8 Gy), fracture of the right humerus (single dose external beam irradiation 8 Gy) and paresis of the hypoglossal nerve. Rapid progression of especially the skeletal metastases, and to a lesser degree the pulmonary metastases, as well as the deterioration of the patient's clinical condition made us re-evaluate the patient for ^{131}I uptake in the tumor and metastases 45 mo after thyroidectomy in a hypothyroid situation. Surprisingly, whole-body retention 2 days after ^{131}I injection was 52%, and 24.7% after 7 days, meaning a 10-fold and 15-fold increase as compared to the previous examination. This increased radioiodine retention was not caused by impaired renal function (kreatinin level 49 μmole/liter; normal range 45–90 μmole/liter).

As shown in Table 1, tumor uptake in the neck and chest area showed significantly higher uptake than in previous examinations. In contrast, the thyroglobulin level was similar to previous measurements (209 pmole/liter). Scinti-

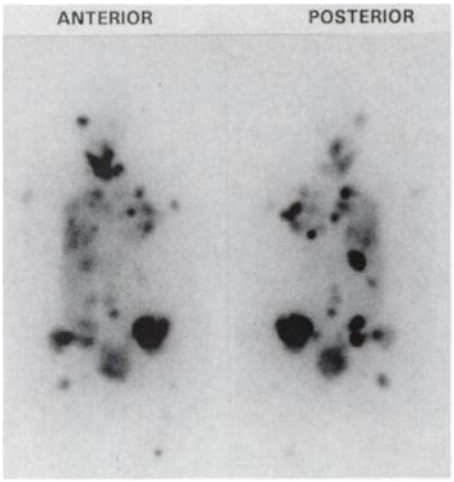

FIGURE 1. Anterior and posterior whole-body images 7 days after i.v. injection of 7.5 GBq ^{131}I. There is extensive metastatic disease in the right orbital region, neck, chest, pelvis, spine and upper arms and legs.

graphic imaging revealed significant ^{131}I uptake in the tumor in the neck and cervical spine and a large number of skeletal and pulmonary metastases (Fig. 1). This was reason to resume treatment with ^{131}I at a dose of 7.5 GBq. Unfortunately, within 3 mo, the patient developed paraplegia due to spine metastasis and was confined to bed. Her medical condition deteriorated very rapidly and she died within 2 wk. This short time span prevented assessment of any response to therapy.

DISCUSSION

With time, decreasing uptake of radioiodine in metastatic differentiated thyroid carcinoma is a well-known phenomenon in the course of the disease. It may be induced or accelerated by ^{131}I treatment (*2,6–8*). Therefore, follow-up studies with radioiodine are often discontinued once ^{131}I uptake has become so low that even under severe hypothyroid conditions no beneficial effects can be expected. In those conditions, palliative external beam irradiation is the only therapeutic option, which is known to be partially effective in anaplastic carcinoma (*2*). Our case indicates, however, that progressive metastases may regain the potential to accumulate radioiodine despite earlier loss of such capacity. Explanation of the reappearing ^{131}I uptake is difficult. Impaired renal function, a known cause for delayed radioiodine excretion, was ruled out. Iodine contamination (e.g., due to intravenous radiographic contrast agents) was excluded as a cause for the previously low ^{131}I uptake. One can hypothesize that progressive metastases and massive tumor growth of the differentiated tumor cells occurred, while the anaplastic, noniodine concentrating cells did not spread. This is not likely to be the sole explanation of the findings in this patient, since it is well known that anaplastic thyroid carcinoma is much more aggressive than differentiated carcinoma. A second explanation may be that carcinoma cells with marginal radioiodine uptake differentiate at some stage during the course of the disease, so that with progressive tumor growth the ^{131}I uptake increases. This last option is supported by repeat CT of the neck area, which indicated stable disease after the last course of external beam radiotherapy, and by the more or less stable condition of the chest abnormalities over the last 2 yr.

In conclusion, disappearance of ^{131}I uptake even just once does not necessarily mean it will be permanent. Therefore, when a progressive metastasis is observed, ^{131}I studies can be reconsidered to assess ^{131}I uptake in the lesions and to decide whether further high dose ^{131}I treatment could be beneficial.

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