Redifferentiation Therapy with Retinoic Acid in Follicular Thyroid Cancer

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We report on a patient with a follicular Hürthle cell carcinoma in whom distant metastases were initially radioiodine negative or only weakly positive. Redifferentiation therapy with 13-*cis* retinoic acid induced a significant radioiodine uptake in metastatic tissue. Thyroglobulin (Tg) immunostaining and autoradiography of a bone metastasis in the right femur, which was initially radioiodine negative, proved Tg synthesis, combined with iodine incorporation into tumor cells. Glucose metabolism in metastases was partially increased and partially unchanged after redifferentiation therapy. The distinct increase of serum Tg after retinoic acid treatment was interpreted as a functional sign of redifferentiation.

Key Words: thyroglobulin; thyroid cancer; redifferentiation therapy; retinoic acid; PET

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In many instances, differentiated thyroid cancer cells lose (partly or completely) their radioiodine uptake capability (*1*). This phenomenon might be addressed as loss of differentiation and has been observed in certain tumor sites during the clinical course and during development from primary tumor to metastases. The absence of radioiodine uptake is associated with a worse prognosis because of the lack of therapeutic options and also because of other parameters related to more aggressive tumor growth of radioiodine-negative carcinomas.

Retinoic acid, known to influence proliferation and to induce differentiation, has been used in various malignant tumors, especially in diseases of the hematopoietic system (*2*). Recently, retinoic acid has been applied successfully in differentiated thyroid carcinoma (*3*).

CASE REPORT

A 67-yr-old woman had undergone surgery in 1945 because of a nontoxic goiter. In 1992, a malignant thyroid tumor was suspected after fine-needle biopsy; total thyroidectomy was performed subsequently. A follicular Hürthle cell tumor (widely invasive growth, primary tumor staging pT 4) was found histologically (Fig. 1A). The operation was followed by a treatment with radioiodine to ablate remnant tissue (1.85 GBq). Distant metastases (liver/ribs) were suspected since 1993 because of high serum thyroglobulin (Tg) levels (around 400 μg/liter) and a faint radioiodine uptake in the lower right thorax, but no metastases could be proven definitely by other imaging modalities (bone scintigraphy, ultrasound, radiography, CT) between 1993 and 1995. The patient was treated three times with high doses (11.1 GBq each) of radioiodine subsequently. In 1995, radioiodine scintigraphy (1.1 GBq) showed only slight uptake in the mediastinum (Fig. 2A) and no uptake in the femur (Fig. 3A). Contamination with "cold" iodine was excluded by measurement of urinary iodine excretion. A whole-body PET scan with fluorodeoxyglucose (FDG) performed 6 mo later revealed areas of abnormally increased glucose metabolism in the lung (two sites), the mediastinum (Fig. 2B) and the right femur (Fig. 3B), suggesting multiple metastases. Sestamibi scintigraphy showed increased tracer uptake in the mediastinum and the right femur (not shown). Subsequently, the patient was treated with 13-*cis* retinoic acid. The recommended dose (1.5 mg/kg body weight) was not tolerated; it was therefore reduced to 0.9 mg/kg body weight. Two months after starting retinoic acid treatment, another treatment with 11.1 GBq radioiodine was performed. Ten days before radioiodine therapy, the retinoic acid dose was reduced again to 0.3 mg/kg body weight. A distinct uptake of radioiodine could be observed in the mediastinum (Fig. 2C), in the lung metastases, in the left shoulder (not shown) and in the right femur (Fig. 3C). After an accident, the patient suffered a fracture of the right femur in the area of the known bone metastasis. The fracture was surgically treated, tumor tissue was removed and osteosynthesis was performed. A second PET study was done 4 wk after the radioiodine therapy. Increased glucose metabolism was observed in multiple lung sites, the mediastinum, the left shoulder, the 10th rib (left side) (Fig. 2D) and the right thigh (not in the femur but in adjacent tissue, probably due to an unspecified increase in metabolism, Fig. 3D). Bone metastases were proven subsequently by bone scintigraphy (not shown). Both PET studies were performed during thyroxine replacement therapy.

Histology of the primary tumor, resected in 1992, showed a differentiated follicular carcinoma with a predominantly trabecular pattern of oxyphilic tumor cells (Fig. 1A). In the bone metastasis, resected in 1995, a follicular tumor of oxyphilic cell type with a mixed follicular and solid pattern was found (Fig. 1B). Tg immunostaining was rather weak in the primary tumor (Fig. 1C), whereas in the metastasis most of the tumor cells stained more intensely (Fig. 1D). Because the radioiodine was administered 3 wk before the study, autoradiography of the metastasis could be performed. The results of both the paraffin block and the slides showed a strong spotlike signal in the tumor (Figs. 1E and 1F).

Serum Tg was close to 100 μg/liter before starting the redifferentiation therapy [thyroid-stimulating hormone (TSH) < 0.1 μU/ml] and increased to 28,000 μg/liter after 5 wk of retinoic acid treatment (TSH < 0.1 μU/ml) and subsequently to > 40,000 μg/liter (measured on day of radioiodine administration; TSH = 38 μU/ml).

DISCUSSION

Several studies have reported that radioiodine-negative differentiated thyroid carcinomas have a poorer prognosis compared to radioiodine-positive carcinomas, due to higher dedifferentiation and therefore higher growth rates, and because patients with these carcinomas cannot be treated with radioiodine (*4,5*). The lack of iodine uptake into tumor cells can occur initially or during the course of the disease (*1*) and is accompanied by a histological dedifferentiation. A preferential destruction of those cells that have the ability to accumulate iodine has to be considered (*6*). In other cases, the primary tumor is well differentiated but (distant or local) metastases are poorly differentiated, particularly if no total thyroidectomy and subsequent ablative radioiodine therapies had been performed (*7*). There are only a few systematic studies comparing primary

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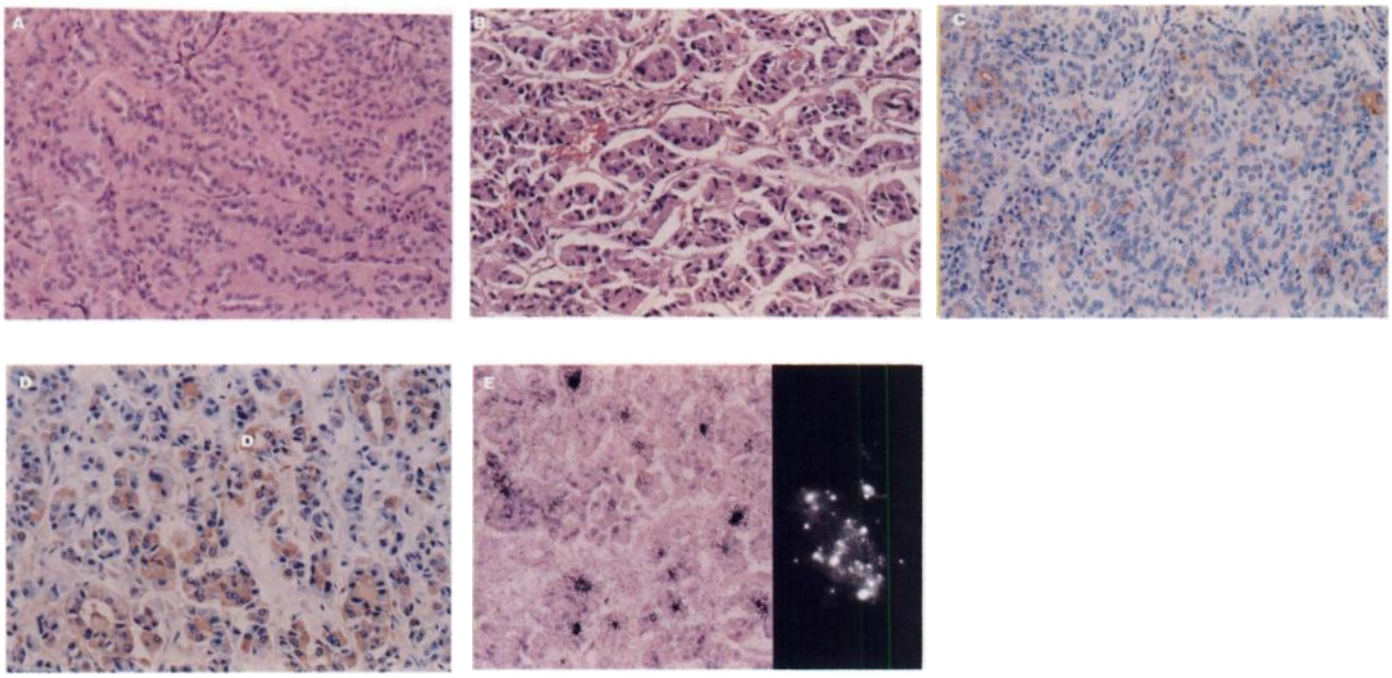

FIGURE 1. (A) Histology of primary tumor (hematoxylin-eosin stain, ×230) showed follicular carcinoma, oxyphilic cell type, with predominantly trabecular pattern. (B) Histology of bone metastasis (hematoxylin-eosin stain, ×230; after retinoic acid treatment) showed follicular carcinoma, oxyphilic cell type and mixed follicular and solid pattern. (C) Immunostaining (antibodies against human thyroglobulin, DAKO diagnostika GmbH, Hamburg, Germany; avidin-biotin complex method, ×230) of primary tumor showed rather weak-positive reaction in most cells, whereas (D) in bone metastasis most of tumor cells stained more intensely. Autoradiography of paraffin material 3 wk after radioiodine administration (bone metastasis) showed intense positive spotlike signal in tumor (E) Paraffin block applied directly to highly sensitive film for 15 hr, ×4. (F) Slide coated with highly sensitive film solution, exposed for 72 hr, counterstained with hematoxylin-eosin, ×230.

tumor and metastases. Harada et al. (*8*) reported that histology differed between primary tumor and metastatic lesions in 36 of 61 patients with thyroid cancer. The authors interpreted their findings as a result of anaplastic or squamous cell transformation from adenocarcinoma. Hürthle cell carcinomas are frequently radioiodine negative, regardless of their grade of differentiation (*1*).

Van Herle et al. (*9*) observed an inhibition of tumor growth and an increase of radioiodine uptake in follicular tumor cells after retinoic acid administration. Activity of type I 5′-deiodinase, which can be addressed as a differentiation marker in thyroid carcinoma, increases after retinoic acid treatment (*10*). Simon et al. (*3*) recently reported the induction of radioiodine uptake in some patients with initially radioiodine-negative, inoperable tumors. They used retinoic acid to induce redifferentiation, which has been engaged in the treatment of other malignant tumors earlier, particularly hematopoietic carcinomas (*2*). In 4 of 10 patients, a positive response (radioiodine uptake) was observed, although no antiproliferative effect of this pharmaceutical could be proven. Among their patients, 1 patient with a partial Hürthle cell-type tumor had a positive response (induction of radioiodine uptake). In the patient discussed in this study, initial poor differentiation of the metastases in the lung, mediastinum and right femur can be suspected because these sites were radioiodine negative or only weakly positive. Nevertheless, decreased radioiodine uptake due to the Hürthle cell type of the tumor cannot be completely ruled out. We decided to try redifferentiation therapy with retinoic acid because effective surgical treatment was impossible due to the spread of metastatic disease. The treatment was well tolerated; only minor side effects (skin dryness) occurred. The post-therapeutic radioiodine scan proved the success of the redifferentiation therapy by showing distinct uptake in metastatic sites, although different radioiodine doses have to be considered. Several tumor cell populations have to be considered, because radioiodine uptake behavior during the clinical course differed between the known tumor sites (e.g., mediastinum versus femur).

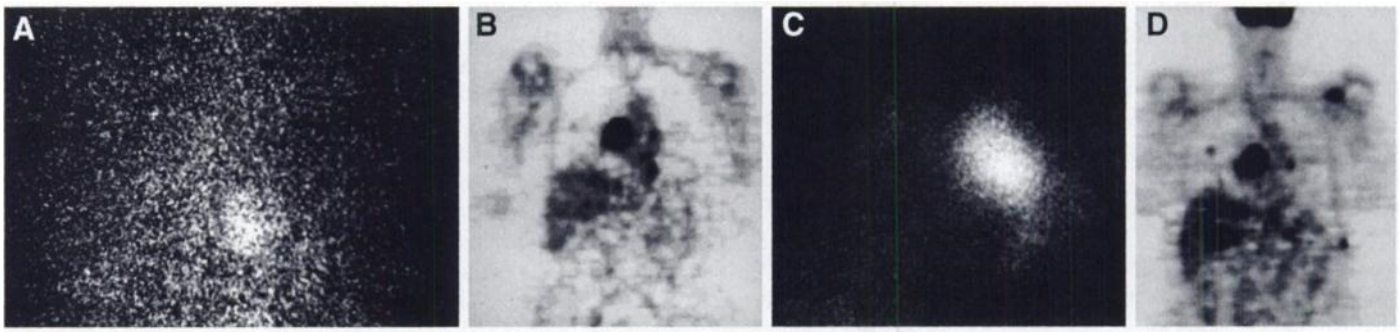

FIGURE 2. Mediastinal metastasis shows marked increase in radioiodine uptake after redifferentiation therapy. (A) Radioiodine scan of thorax, posterior view, before treatment with retinoic acid; thyroid-stimulating hormone (TSH): 25 μU/ml; radioiodine amount: 1.1 GBq. (C) Identical view as A after treatment with retinoic acid; TSH: 38 μU/ml; radioiodine amount: 11.1 GBq. FDG PET revealed high glucose utilization values in mediastinum, lung metastases, left shoulder and 10th rib (left side). (B) Coronal FDG PET slice, patient's left side is on the right, before retinoic acid treatment. (D) Identical slice as B after treatment with retinoic acid.

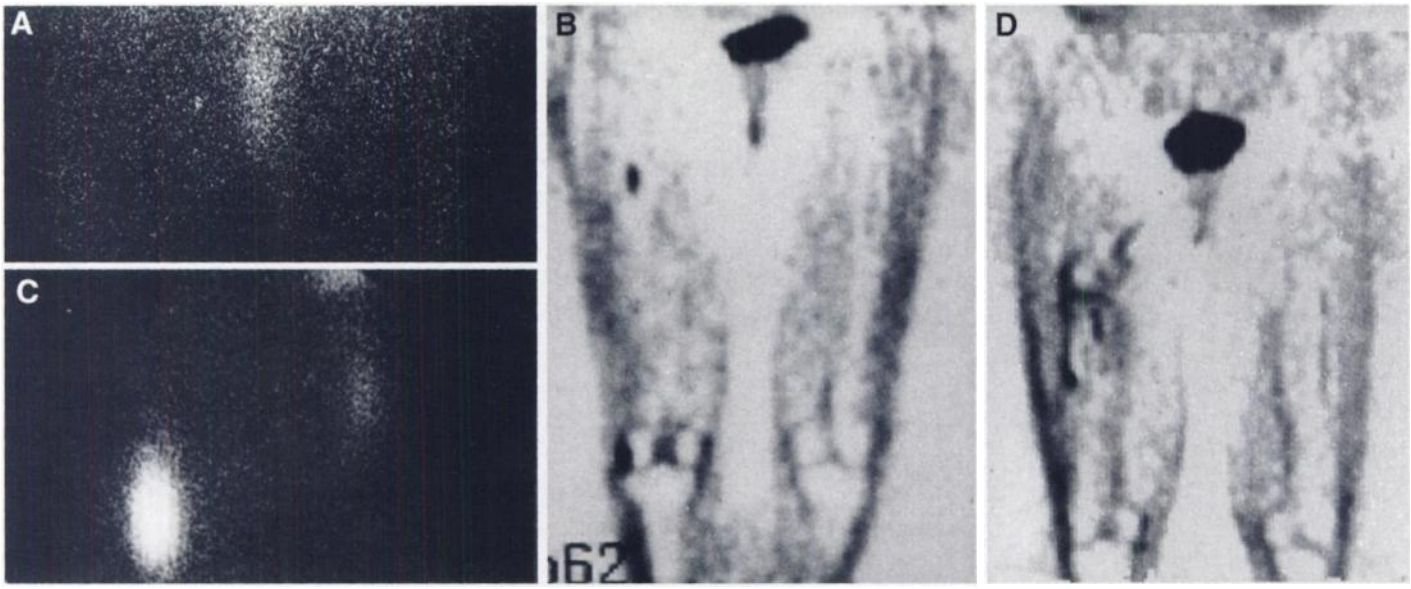

FIGURE 3. Bone metastasis in right femur was initially radioiodine negative. (A) Radioiodine scan of femur, anterior view, before treatment with retinoic acid; thyroid-stimulating hormone (TSH): 25 μU/ml; radioiodine amount: 1.1 GBq. Redifferentiation therapy induced distinct radioiodine uptake at this metastatic site. (C) Identical view as A after treatment with retinoic acid; TSH: 38 μU/ml; radioiodine amount: 11.1 GBq. Metastasis was FDG positive before treatment. (B) Coronal FDG PET slice, patient's left side is on the right, and PET scan after surgical removal showed only nonspecific tracer uptake in adjacent tissue of right thigh. (D) Identical slice as B after surgery.

Because of the femur fracture, we were able to compare histology of the primary tumor before and of one bone metastasis after treatment with retinoic acid. By comparing the conventional histology from the primary tumor with that from the metastasis, a slightly different growth pattern of the oxyphilic tumor cells could be observed, but cellular differentiation did not change significantly. Both the primary tumor and the metastasis fulfilled the morphologic criteria of a differentiated follicular carcinoma (*11*). Immunohistochemically (in parallel staining), the positive reaction was more intense in the metastatic tumor than in the primary tumor. Nevertheless, immunostaining has only limited—if any—use in quantification. Autoradiography could prove the radioiodine uptake in parts of the tumor by showing an intense signal. Ahuja et al. (*12*) reported heterogeneous radioiodine uptake (^{125}I incubation in culture solution) in thyroid tissue, with small follicles showing the highest uptake. Other parameters that also influence radiopharmaceutical uptake have to be considered, e.g., local perfusion. One can speculate that radioiodine uptake on a microscopic level as well as high-positive Tg immunostaining was induced in former iodine-negative cells by the redifferentiation therapy. Nevertheless, Oyen et al. (*13*) published a report on one patient with a spontaneous reappearance of radioiodine uptake in metastases, with no reasonable explanation for the observed phenomenon. This phenomenon, although rare, cannot be ruled out in the patient in this study.

Local glucose use, as measured by FDG PET imaging, is an indicator of malignancy. In thyroid carcinoma, FDG uptake is correlated with the grade of malignancy (*14*), and most malignant lesions are only FDG positive (poorly differentiated tumors) or radioiodine positive (well-differentiated tumors) (*14,15*). In the patient described here, FDG uptake in metastatic lesions did not vanish during redifferentiation therapy but was unchanged in lung and mediastinum and increased in the left shoulder. One can suspect that FDG uptake in metastatic lesions would be even more increased without retinoic acid treatment due to a natural progression of the disease, but an activation of prenecrotic tumor cells, which have been shown to be responsible for FDG uptake (*16*), by retinoic acid has to be considered. In a direct comparison of autoradiographic accumulation patterns of [^{14}C]deoxyglucose (DG) and histopathologic examinations, Kubota et al. (*17*) found that the uptake of [^{14}C]DG was higher in the granulation tissues surrounding necrosis than in viable tumor cells of trabecular-growing and follicle-forming tissue. Börner et al. (*18*) reported on the clinical course of eight patients, including sequential FDG PET imaging during redifferentiation therapy. They found a decrease of glucose use in six of these eight patients after treatment combined with a cessation of serum-Tg increase. In contrast to this study, they did not observe an induction of radioiodine uptake with therapeutic relevance.

In the patient discussed here, serum Tg was dramatically increased during retinoic acid treatment from values of approximately 100–28,000 μg/l (on levothyroxine therapy) and >40,000 μg/l (off levothyroxine therapy). This increase demonstrates an overall deterioration (tumor growth), but it appears more likely that it proves the restoration of Tg synthesis uptake capability during redifferentiation. Because distribution of Tg synthesis in metastases on the microscopic level is unknown before retinoic acid treatment, the course of serum Tg values has to be used as a parameter, suggesting that Tg synthesis in metastatic tissue was enhanced by redifferentiation therapy.

CONCLUSION

Histopathology showed that no morphologic cellular dedifferentiation occurred in the metastasis, that Tg expression was probably improved (with the limitations mentioned above) and that radioiodine uptake was demonstrated directly in the tumor tissue. These results may be interpreted as signs of functional redifferentiation. Treatment with retinoic acid before high-dose radioiodine therapy should be considered in radioiodine-negative (or weakly positive) metastases, particularly in bone metastases of follicular tumors, since in patients with these tumors complete remission usually cannot be achieved, even with high radioiodine doses (*19*).

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Remotely Pollable Geiger-Müller Detector for Continuous Monitoring of Iodine-131 Therapy Patients

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In many countries, patients treated with therapeutic amounts of ^{131}I are hospitalized because of radiation safety considerations. To determine when they can return home, radiation levels are intermittently monitored at bedside using a handheld Geiger-Müller (GM) counter, although this procedure can be cumbersome and inexact. **Methods:** We have developed and tested a remotely pollable system for continuous radiation monitoring of ^{131}I therapy inpatients, using readily available hardware and standard telephone lines. The remote detector system, consisting of a palmtop IBM-compatible personal computer, specialized software, PCMCIA modem and miniature serial port-based GM detector, is placed opposite the patient's bed at a fixed distance, and continuous 1-min acquisitions are started. Initially and at least twice daily, the remote palmtop is contacted by modem, and all interval data are uploaded onto the operator's base computer over the telephone line, including measurements taken with the patient in a predetermined standardized position. Continuous minute-to-minute data may be viewed in native form or can be imported into graphing and spreadsheet programs. Points acquired with the patient in standardized position are specially marked to highlight the constant geometry used. The ratio of initial counting rate to administered dose is used to estimate residual ^{131}I body burden by proportionality. Display of data as a semilogarithmic plot facilitates extrapolation of the activity curves and prediction of the patient's earliest time of discharge. **Results:** We have characterized the remote GM detector system to confirm accuracy, counting rate linearity and reliability of data transfer. We describe examples that illustrate the applicability and usefulness of this method for remote monitoring of inpatient ^{131}I therapy levels. **Conclusion:** Monitoring patients with the described remotely pollable GM detector is an accurate and easy-to-implement technique that could conceivably lead to shortened hospital stays for ^{131}I therapy inpatients. Continuous quantitative data obtained are useful for kinetic and dosimetric analyses, which may be applied to study other gamma-emitting radiopharmaceuticals as well. The flexibility of the technique may permit its use in the monitoring of therapy on an outpatient basis, where allowed.

Key Words: Geiger-Müller detector; remote monitoring; iodine-131 therapy

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Radioactive ^{131}I is an effective and established mode of therapy for thyroid neoplasia (*1,2*). An accepted tenet of radiation safety is that benefit afforded to patients by therapeutic administration of ^{131}I must be balanced by societal considerations regarding radiation exposure to individuals who do not derive direct gain, such as family members, coworkers and incidentally exposed persons (*3–5*). To address this concern, most national regulatory agencies have required segregation and hospitalization of patients who receive what is defined as a significant amount of radionuclide. For example, in the United States, patients receiving 1110 MBq (30 mCi) or more of ^{131}I have, until recently, been confined to the hospital (*6*), resulting in an estimated 15,000 admissions annually (Mallinckrodt, Inc., personal communication). These regulations were revised based on predicted exposure rates to family members, to limit the likely exposure of other individuals to no more that 5 millisieverts (0.5 rem) (*7*). The allowable body burden of ^{131}I at discharge is unique to each patient and depends on the family situation and the patient's need for supportive care (*8*). In many

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