

Somatostatin Receptor Expression in Hürthle Cell Cancer of the Thyroid

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Somatostatin receptor expression, which was not a previously described marker for Hürthle cell cancer of the thyroid, was demonstrated by in vivo imaging with ^{111}In -pentetreotide in three patients. This phenomenon not only adds another imaging technique to the nuclear medicine armamentarium for detecting recurrent and metastatic cancer in patients with Hürthle cell cancer but also opens up an alternative therapeutic avenue with somatostatin analogs or their radiolabeled compounds.

Key Words: Hürthle cell cancer; somatostatin receptors; indium-111-pentetreotide; thyroid cancer

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Hürthle cell tumors of the thyroid are neoplasms composed exclusively or predominantly (over 75%) of oncocyctic follicular cells. Hürthle cells originate from follicular cells as evidenced by an intact thyroid stimulating hormone (TSH) receptor-adenylate cyclase system, which remains functional in the neoplastic state. Hürthle cell tumors are identified by the presence of cells with an abundant granular cytoplasm attributable to a large number of mitochondria ultrastructurally.

Carcangiu et al. (1) classify these neoplasms as malignant, intermediate or benign based on the presence and degree of capsular and vascular invasion, pattern of growth (follicular, trabecular or solid), nuclear atypia and necrosis. Malignant Hürthle cell tumors comprise 18% of Hürthle cell neoplasms of the thyroid and account for 2%-3% of all patients with thyroid cancer.

As in all other types of thyroid cancer, all aspects of patient management including extent of initial surgery, the role of radioactive iodine treatment and appropriate metastatic workup are controversial in Hürthle cell cancer (2-4). The oncocyte phenotypic differentiation in Hürthle cell cancer has not only morphologic significance, but also connotes metabolic and biologic behavior differences which justify categorizing of these tumors as a different clinical entity. The number of patients who die of Hürthle cell cancer is approximately 10 times that of patients dying from papillary or follicular cancers (5). Radioactive iodine uptake of Hürthle cell cancers is minimal and probably due to the uptake in the follicular component (6). As a consequence, the clinical role of radioactive iodine treatment is largely limited to postsurgical ablation. The rationale for ablation is the fact that the Hürthle cell

phenotype usually preserves the thyroglobulin production capacity and, thus, thyroglobulin can be used as a tumor marker for metastatic/recurrent disease after radioactive iodine ablation.

A prominent subcellular marker of Hürthle cells is the large number of mitochondria, which is the reason why $^{99\text{m}}\text{Tc}$ -sestamibi localization is particularly useful for these tumors. Nonspecific tumor localization also can be achieved using ^{201}Tl -chloride and $^{99\text{m}}\text{Tc}$ -pentavalent DMSA (7,8).

Hürthle cell tumors have neither the morphologic features nor the classical histochemical markers which characterize neuroendocrine differentiation. Hürthle cell carcinomas in the three patients discussed in this article were shown to express varying degrees of somatostatin receptor expression on in vivo ^{111}In -pentetreotide (octreoscan) imaging.

CASE REPORT

Patients

Patient 1 is a 65-yr-old man with a history of a 1-cm left thyroid lobe nodule presented in 1976, the pathology of which was initially reported as benign. The diagnosis of Hürthle cell cancer was made after two subsequent thyroidal recurrences which led to left and right subtotal thyroidectomies in 1983 and 1985, respectively. In 1989, he presented with right cervical nodal disease and had a total thyroidectomy with right radical neck dissection. The patient received radiation therapy to the neck for nodal recurrence in 1990. He developed lung metastases in 1993. He was given three radioactive iodine treatments (2220 MBq (60 mCi) in June 1993, 2960 MBq (80 mCi) in December 1993 and 3700 MBq (100 mCi) in April 1994) with no clinical response.

The patient was referred to the University of Miami in August 1996 for further evaluation and treatment. He complained of pain, pressure and occasional spasms in the neck as well as some difficulty in swallowing. He did not have any respiratory symptoms or signs. The CT scan showed bilateral macronodular lung disease and mediastinal nodal disease. A $^{99\text{m}}\text{Tc}$ -sestamibi scan showed positive localization in all thoracic lesions. The patient had whole-body ^{123}I imaging with 10 mCi with a TSH level of 77 uIU/ml and plasma iodine level of 2.1 mcg/dl. There was no radioactive iodine uptake in any of the lesions.

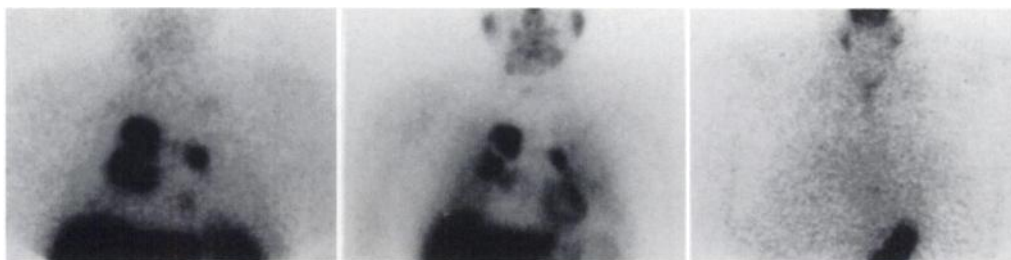
Indium-111-pentetreotide imaging was performed to assess the somatostatin receptor status of the tumor. Intense tracer uptake was noted in all the lesions with a tumor-to-background ratio of 19:1 at 24 hr postinjection (Fig. 1).

Patient 2 is a 61-yr-old man with a history of left thyroid lobectomy who presented in 1975. The pathology was initially reported as benign. The patient incidentally was found to have

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FIGURE 1. Tumor localization studies performed on Patient 1. (Left) Indium-111-pentetreotide image with 222 MBq (6 mCi) shows intense tumor uptake with tumor-to-background radiation of 19:1. (Middle) Technetium-99m-sestamibi image with 740 MBq (20 mCi) shows a similar pattern of uptake. (Right) Iodine-123 image with 370 MBq (10 mCi) shows no uptake in the tumor.



metastatic lung nodules before an emergency hand surgery in 1995. He had left upper lobe lung resection for a large nodule. The pathology of the resected nodule and the review of the original thyroid pathology revealed Hürthle cell cancer of thyroid.

The patient had a complete thyroidectomy with bilateral modified radical neck dissection at the University of Miami in August 1995. He received 5550 MBq (150 mCi) ^{131}I for remnant ablation in October 1995. The follow-up CT scan in March 1996 showed stable lung nodules. Thyroglobulin was 68 ng/ml and the $^{99\text{m}}\text{Tc}$ -sestamibi scan was negative. The patient had whole-body ^{123}I imaging with 370 MBq (10 mCi) with a TSH level of 50 uIU/ml. No radioactive iodine uptake was noted in the lungs. Indium-111-pentetreotide imaging showed uptake in the lungs with a tumor-to-background ratio of 3:1 at 24 hr postinjection.

Patient 3 is a 68-yr-old man who initially presented with a mass in the left lobe of the thyroid in 1987. He had a left lobectomy and the pathology proved to be Hürthle cell cancer with positive margins. He had a completion thyroidectomy shortly thereafter. The initial metastatic work-up was negative, and the patient remained disease-free until January 1995 when he presented with a cervical lymph node and scalp metastases, both of which were excised. Further diagnostic work-up revealed mediastinal metastasis. Radiation therapy was given to the scalp tumor bed (3500 cGy) and the left neck and mediastinum (4500 cGy) in September 1995. There was no clinical evidence of response after the radiation therapy.

The patient was referred to the University of Miami in March 1996 for further evaluation and treatment. He complained of nonproductive cough and mild dysphagia. The CT scan showed multiple mediastinal nodal disease. Thyroglobulin was 125 ng/ml and the $^{99\text{m}}\text{Tc}$ -sestamibi scan showed positive localization in the mediastinum and both hila. The patient had whole-body ^{123}I imaging with 370 MBq (10 mCi) with a TSH level of 70 uIU/ml and plasma iodine level of 1.6 mcg/dl. A fairly intense uptake was noted in the thyroid remnant. However, there was only a faint uptake in the mediastinum. Dosimetry revealed a bone marrow absorbed dose of 0.5 rad/mCi, and the patient was treated with 14,800 MBq (400 mCi) ^{131}I in June 1996. No clinical response was observed at 8 wk post-treatment. Indium-111-pentetreotide imaging showed intense tracer uptake in the mediastinal and hilar lesions with a tumor-to-background ratio of 7:1 at 24 hr postinjection.

DISCUSSION

Therapeutic alternatives for metastatic Hürthle cell cancer are limited. Two-thirds of patients with metastases have disease outside the neck, which is not amenable to surgical treatment. Chemotherapy is not known to be effective, and radiation therapy is of little help. Radioactive iodine uptake is minimal, and this modality is ineffective. There is a need for new therapeutic modalities to control these tumors.

The occurrence of somatostatin receptor expression in other non-neuroendocrine tumors is well documented. The best known examples include breast cancer, non-small-cell lung cancer and lymphomas (9–13). Somatostatin is known to

interfere with the signal transduction mediating cellular proliferation and neoplastic growth (14). Somatostatin analogs have been successfully used to inhibit tumor growth in experimental models (15). A pilot study of the effect of octreotide on tumor control in thyroid cancer patients failed to demonstrate any antitumor efficacy (16). This small series included one patient with Hürthle cell cancer. Studies are underway using high doses of ^{111}In -pentetreotide or other somatostatin analogs labeled with ^{90}Y for detecting unfavorable neuroendocrine and non-neuroendocrine tumors.

Hipkin et al. (17) demonstrated an internalization phenomenon of an agonist-receptor complex with a receptor Type II specific ^{125}I -labeled somatostatin analog. This finding might constitute the basis of the Auger electron reliant effect of ^{111}In -pentetreotide.

The degree of receptor expression, as measured by the semiquantitative technique we used, was quite variable in the three cases presented in this article. The highest uptake of ^{111}In -pentetreotide was observed in Patient 1, who had the largest volume disease and had no radioactive iodine uptake. The lowest uptake was observed in Patient 3, who had micronodular lung disease with lesions ranging from 0.4 cm to 0.8 cm. This volume was probably below the resolution limits of the technique at the diagnostic dose used. Negative $^{99\text{m}}\text{Tc}$ -sestamibi imaging also may have been due to this limitation.

Somatostatin receptor expression has not previously been reported in Hürthle cell thyroid cancer. The presence of somatostatin receptors on malignant Hürthle cells suggests that imaging and treatment with somatostatin analogs may be of value.

Studies exploring the factors involved in receptor expression, methods of receptor up-regulation and dosimetric studies to evaluate tumor kinetics of radiolabeled somatostatin analogs are warranted for designing effective radioreceptor therapy trials.

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Glucose Transporter Protein-Independent Tumor Cell Accumulation of Fluorine-18-AFDG, a Lipophilic Fluorine-18-FDG Analog

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Fluorine-18-fluorodeoxyglucose (FDG) is used clinically for tumor diagnosis, but its mechanism of accumulation in tumor cells is complicated because two factors, glucose transporter protein (GLUT) and hexokinase, govern [^{18}F]FDG uptake directly. We selected a lipophilic [^{18}F]FDG analog, 1,3,4,6-tetra-acetyl-2- ^{18}F -2-deoxy-D-glucose ([^{18}F]AFDG), to regulate the effects of hexokinase and evaluated its characteristics in an in vitro cell culture system. **Methods:** Fluorine-18-AFDG was synthesized by the method used to produce [^{18}F]FDG, as an intermediate of [^{18}F]FDG. Fluorine-18-AFDG uptake study was performed with LS180 tumor cells, and its metabolites were also investigated by thin-layer chromatography. To evaluate the relationship between [^{18}F]AFDG and GLUT, we also examined [^{18}F]AFDG uptake in the presence of cytochalasin B or with increased medium glucose concentration. The effects of lowered temperature (4°C) on [^{18}F]AFDG uptake were also investigated. **Results:** Fluorine-18-AFDG (lipophilicity: octanol/water = 3.5) uptake was 3.3-fold higher than that of [^{18}F]FDG. Metabolic analysis showed that [^{18}F]AFDG was extremely stable in the incubation medium but was quickly hydrolyzed and metabolized to 2-fluoro- ^{18}F -2-deoxy-D-glucose-6-phosphate ([^{18}F]FDG-6P) in tumor cells. Fluorine-18-FDG-6P accounted for approximately 45% of the total radioactivity after a 60-min incubation of [^{18}F]AFDG. Incubation with 50 μM cytochalasin B did not affect [^{18}F]AFDG uptake. In medium with double the control glucose level, [^{18}F]FDG uptake was decreased by about 50%, but [^{18}F]AFDG uptake was not affected. Fluorine-18-AFDG uptake and [^{18}F]FDG-6P production did not show saturation and increased linearly with addition of a 10-fold higher concentration of [^{18}F]AFDG. Lowered incubation temperature caused decreased [^{18}F]AFDG uptake due to reduced [^{18}F]FDG-6P production. **Conclusion:** Fluorine-18-AFDG rapidly penetrated the cell membrane as a result of its high lipophilicity and was metabolized to [^{18}F]FDG-6P within cells. Fluorine-18-AFDG was thus characterized as "GLUT-independent [^{18}F]FDG."

Key Words: glucose metabolism; deoxyglucose; cultured tumor cells; glucose analogs; hexokinase

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Tumors generally have high glycolytic activity (1-4). Based on this characteristics, PET with ^{18}F -fluorodeoxyglucose (FDG) has become a clinically useful tool for tumor imaging

because of its high sensitivity and high specificity (5,6). The entrance of [^{18}F]FDG is mediated by glucose transporter proteins (GLUTs), and [^{18}F]FDG is then metabolized to [^{18}F]FDG-6-phosphate by hexokinase. In general, [^{18}F]FDG-6P cannot be further metabolized, so that ^{18}F radioactivity is retained as [^{18}F]FDG-6P in the cells. In the brain, glucose metabolism is believed to be governed by hexokinase. Based on this consideration, quantification of the glucose metabolic rate has been performed with [^{18}F]FDG (7,8).

On the other hand, the contribution of hexokinase to the accumulation of [^{18}F]FDG in tumors is not similar to that in the brain. High hexokinase activity in tumors has been reported (9-11), but decreased phosphatase activity (12) and increased GLUT expression (13-16) are also considered to be the cause of [^{18}F]FDG accumulation in tumors. In addition, hypoxic conditions, such as low oxygen supply due to poor perfusion, are thought to enhance glycolytic metabolism (17,18), and high [^{18}F]FDG accumulation in "hypoxic tumor cells" has been reported in accordance with increased GLUT expression (19). Thus, it is difficult to use [^{18}F]FDG accumulation to monitor glucose metabolic rate of tumors, based on hexokinase activity.

Monitoring accumulation of a membrane-permeable [^{18}F]FDG analog with considerable affinity to hexokinase might be a better parameter for the evaluation of glucose metabolism in tumors. We selected 1,3,4,6-tetra-acetyl-2- ^{18}F -2-deoxy-D-glucose ([^{18}F]AFDG) as a candidate for such a molecule (its structure is shown in Fig. 1). In this study, an in vitro cell culture system was used to determine whether [^{18}F]AFDG instantly penetrates the cell membrane due to its high lipophilicity, whether [^{18}F]AFDG is hydrolyzed to [^{18}F]FDG after penetration and whether [^{18}F]FDG produced from [^{18}F]AFDG is phosphorylated by hexokinase and retained in the cells. Based on these considerations, the possibility of use of [^{18}F]AFDG as a tracer for monitoring tumor glucose metabolism will be discussed.

MATERIALS AND METHODS

Fluorine-18-FDG and Fluorine-18-AFDG Synthesis

Fluorine-18-FDG and its intermediate [^{18}F]AFDG were produced by the method of Hamacher et al. (20) with an automated [^{18}F]FDG synthesis system (NKK Co. Ltd., Tokyo, Japan). Briefly, ^{18}F anion, synthesized from [^{18}O]H₂O in the reaction $^{18}\text{O}(\text{p,n})^{18}\text{F}$,

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