one ^{18}F-FU study 120 min postinjection is required, and the radiotracer reflects the distribution of the cytostatic agent and the trapping which is predictive to therapy outcome.

CONCLUSION

Studies with ^{18}F-FU in patients with metastatic colorectal carcinomas have shown, that PET is a suitable tool for pharmacokinetic studies, since ^{18}F-labeled FU is identical to the nonlabeled agent. In this study, we compared the trapping of ^{18}F-FU in liver metastases before onset of chemotherapy with the tumor growth rate as measured by CT follow-up studies within 3–11 mo after initiation of FU chemotherapy. Only lesions with an enhanced trapping of ^{18}F-FU (120 min postinjection) exceeding 3.0 SUV responded to therapy. A significant correlation of 0.86 ($p < 0.001$) was found between the ^{18}F-FU trapping and the tumor growth rate. PET with ^{18}F-FU and a single measurement 120 min postinjection before onset of chemotherapy helps to identify responders and nonresponders and, therefore, predict therapy effect.

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Severe Thyrotoxicosis Due to Functioning Pulmonary Metastases of Well-Differentiated Thyroid Cancer

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We report two cases of thyrotoxicosis resulting from hyperfunctioning lung metastases from differentiated thyroid cancer. In both patients, a simultaneous diagnosis of thyrotoxicosis and metastatic thyroid cancer was made, based on thyroid function tests as well as ^{131}I whole-body scans showing low thyroid uptake of radioiodine and multiple foci of intense ^{131}I uptake in the lungs. After total thyroidectomy (performed in Patient 2 only) and ^{131}I therapy (cumulative dose of 12.3 GBq in Patient 1 and 9.6 GBq in Patient 2), there was a rapid clinical improvement with significant reduction of the pulmonary metastatic disease in both patients: Patient 1 became euthyroid, while Patient 2 became hypothyroid. Analysis of the 54 cases reported in the literature, including the 2 cases described here, shows this to be a very rare cause of thyrotoxicosis and one that can pose serious problems for both the diagnostic evaluation and choice of therapeutic strategy when compared with the much more common nonhyperfunctioning metastases from thyroid cancer. Lesser degrees of thyroid hormone secretion by differentiated thyroid cancer may be detected and exploited diagnostically by the chromatographic analysis of serum for endogenously labeled thyroid hormones after ^{131}I administration.

Key Words: thyrotoxicosis; differentiated thyroid cancer; lung metastases; iodine-131 therapy

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Thyrotoxicosis resulting from functioning metastatic thyroid cancer is rare. In 1946, Leiter et al. (*1*) described the first

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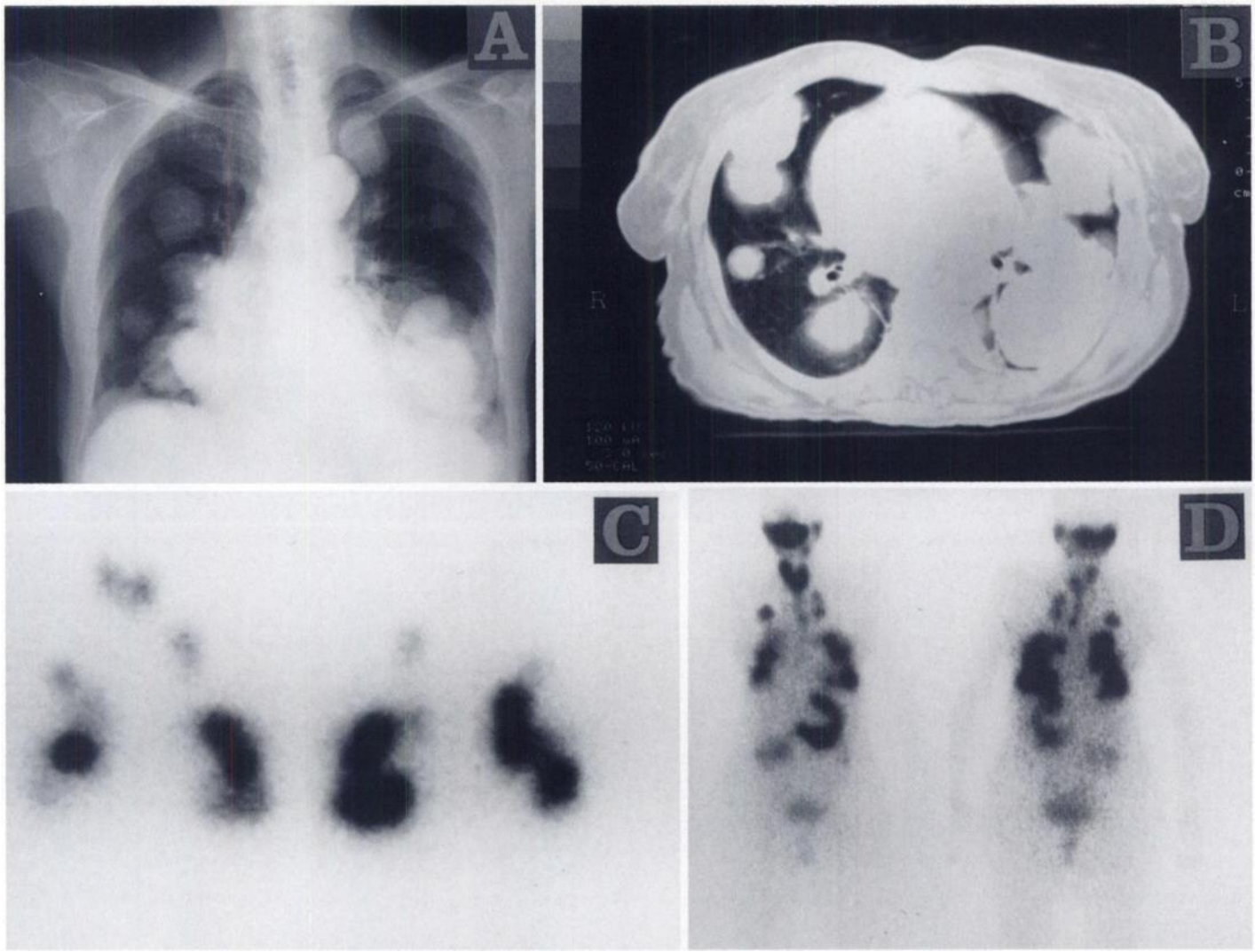

FIGURE 1. (A) Chest radiograph and (B) chest CT demonstrate numerous macronodular pulmonary metastases and associated findings of severe chronic obstructive pulmonary disease in both lungs. (C) Iodine-131 scintigraphy of neck and chest in anterior and posterior projections shows residual thyroid tissue and intense, bilateral, focal pulmonary accumulation of radioiodine. (D) Technetium-99m-pertechnetate whole-body scan in anterior and posterior projections also demonstrates trapping of pertechnetate in residual thyroid tissue and in pulmonary lesions.

patient with hyperthyroidism due to metastatic thyroid cancer, and 52 cases of this syndrome have been reported (*2,3*).

This type of extrathyroidal thyrotoxicosis may present confusing diagnostic problems. Once the disease has been diagnosed, therapy must be directed toward both treating the thyrotoxicosis and curing the neoplastic disease.

We present two cases of well-differentiated thyroid cancer with hyperfunctioning lung metastases causing thyrotoxicosis, review the literature and discuss the autonomous biosynthesis and secretion of thyroid hormones by differentiated thyroid cancer as a phenomenon that can be exploited for diagnosis.

CASE REPORTS

Patient 1

A 69-yr-old woman presented at Catholic University of the Sacred Heart in Rome with small diffuse goiter, overt thyrotoxicosis (weight loss, hand tremor, heat intolerance, insomnia and palpitations) and pulmonary insufficiency manifesting as dyspnea, hypoxia and hypercarbia. She had, 25 yr before, undergone a partial thyroidectomy (the pathological diagnosis of which was unknown).

Thyroid function tests showed thyroid-stimulating hormone (TSH) <0.06 mU/liter (normal, 0.36–3.25 mU/liter), T3 = 358 ng/dL (normal, 52–160 ng/dL), T4 = 13.1 μg/dL (normal, 4.2–11 μg/dL), FT3 = 10.4 pg/ml (normal, 1.9–5.6 pg/ml) and FT4 = 3.8 ng/dL (normal, 0.7–1.8 ng/dL).

A ^{131}I thyroid scan after 1.85 MBq showed low and patchy uptake of the tracer in the thyroid bed with no scintigraphic evidence of hyperfunctioning nodules or Graves' disease. The ^{131}I thyroid uptake in the neck was 5.3% at 6 hr and 5.5% at 24 hr. The intake of exogenous iodine and thyroid hormones was ruled out. An ultrasound study of the neck revealed a small amount of diffuse micronodular hyperplasia in the residual thyroid tissue.

The chest radiograph showed multiple bilateral macronodular metastases and changes consistent with chronic obstructive pulmonary disease (Fig. 1A). These findings were better defined by a CT scan performed without iodinated contrast media (Fig. 1B). A ^{131}I whole-body scan performed 24 hr after administration of 74 MBq confirmed the low thyroid uptake of radioiodine but demonstrated multiple foci of intense radioiodine uptake in both lungs due to ^{131}I-avid pulmonary metastases (24-hr lung uptake was 46%; Fig. 1C). Better definition of the number and extent of metastases was then obtained by means of a 370-MBq ^{99m}Tc-pertechnetate whole-body scan (Fig. 1D).

The serum thyroglobulin level (Tg), assayed by immunoradiometric assay methodology on a diluted sample, was 48,680 ng/mL (normal <85 ng/mL). Serum thyroid-stimulating immunoglobulins (TSI) were 8.2 IU/liter (normal, 1–10 IU/liter).

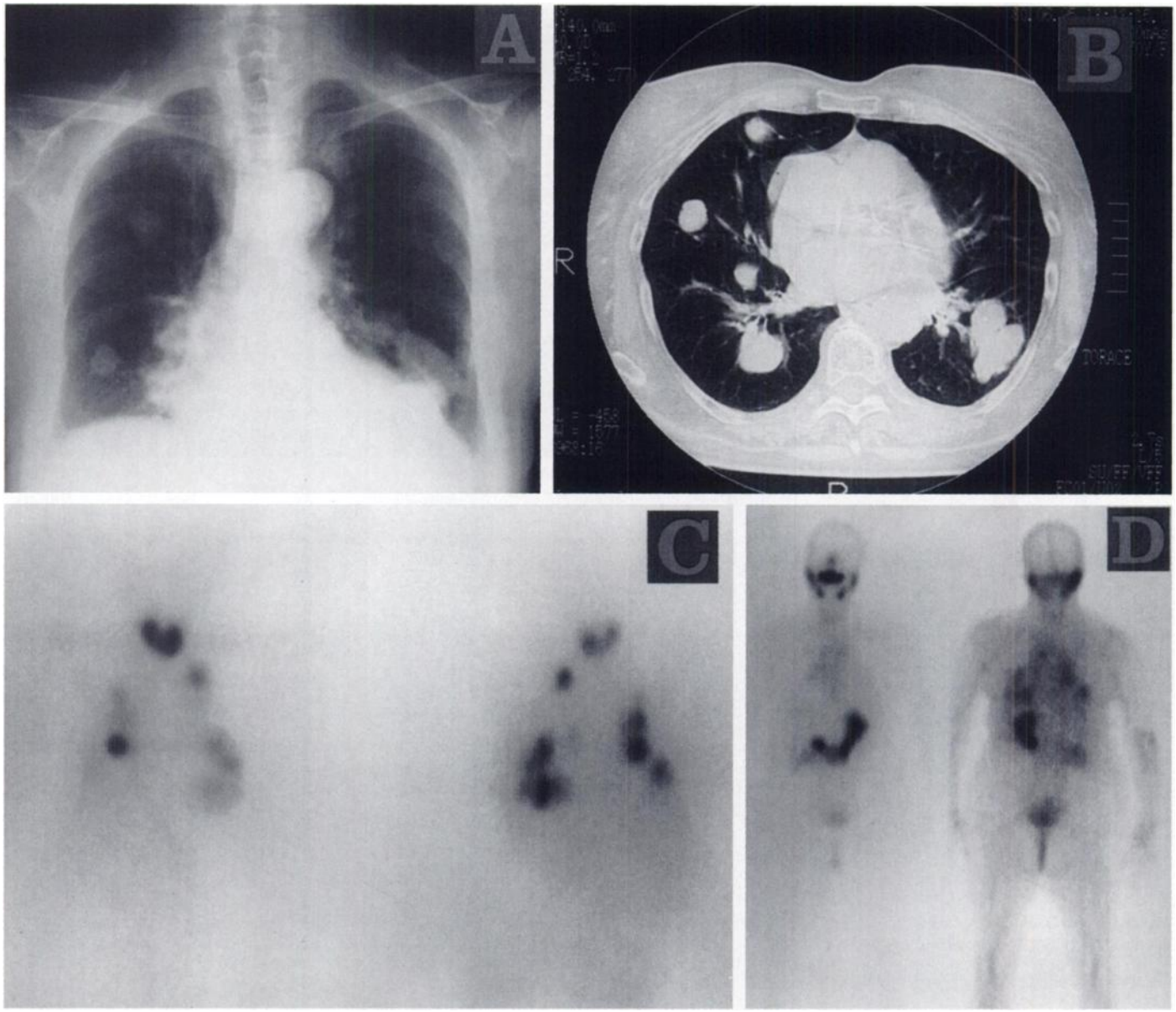

FIGURE 2. (A) Chest radiograph, (B) chest CT and (D) ^{99m}Tc-pertechnetate whole-body scan performed 6 mo after second radioactive iodine therapy. Note marked reduction in number and size of pulmonary metastases. (C) Iodine-131 whole-body scan demonstrated less-striking reduction in uptake.

The aforementioned data led to a diagnosis of thyrotoxicosis with low thyroid radioiodine uptake sustained by hyperfunctioning pulmonary metastases. A total thyroidectomy was not performed due to the poor clinical condition of the patient, who had pulmonary failure (PO_2 = 43.6 mmHg; PCO_2 = 47.2 mmHg) that required permanent O_2 treatment, low thyroid bed ^{131}I uptake and intense ^{131}I uptake by the pulmonary metastases.

Two therapeutic doses of radioiodine (cumulative dose of 12.3 GBq with an interval of 5 mo) were given to treat both the thyrotoxicosis and pulmonary metastatic disease. Before the first ^{131}I therapy, the patient was treated for 4 wk with propylthiouracil (450 mg/day) and methylprednisolone (80 mg/day) to prevent possible thyrotoxic storm (*4*).

Follow-up, obtained 6 mo after the last radioiodine therapy by means of a chest radiograph, CT scan and ^{99m}Tc-pertechnetate whole-body scan (Fig. 2A, B, D), indicated a significant improvement of the pulmonary metastatic disease. Although this was less evident on the qualitative ^{131}I whole-body scan evaluation (Fig. 2C), the 24-hr ^{131}I lung uptake had decreased to 13% and Tg had decreased to 13,000 ng/mL (28% and 27% of the original values, respectively). Thyroid hormone levels and TSH were normal even after antithyroid therapy had been discontinued (TSH = 0.4 mU/liter; T3 = 125 ng/dL; T4 = 6.5 μg/dL; FT3 = 2.2 pg/ml; FT4 = 0.7 ng/dL). The patient had gained 10 kg in weight, the symptoms of thyrotoxicosis had completely resolved, she was no longer dyspneic and the arterial blood gases had significantly improved (PO_2 = 61 mmHg; PCO_2 = 35 mmHg). Further ^{131}I therapy has been planned and will be performed in 8 mo.

Patient 2

A 79-yr-old woman was admitted to the Department of Nuclear Medicine in Busto Arsizio Hospital with a large multinodular goiter, arterial hypertension (210/100 mmHg), overt thyrotoxicosis with weight loss, atrial fibrillation as well as pulmonary insufficiency (PO_2 = 38.4 mmHg; PCO_2 = 53.3 mmHg) and congestive heart failure. Thyroid function tests revealed TSH <0.06 mU/liter (normal, 0.36–3.25 mU/liter), T3 >1,000 ng/dL (normal, 80–180 ng/dL), T4 = 29.5 μg/dL (normal, 4.5–11.7 μg/dL), FT3 = 10.4 pg/ml (normal, 1.9–5.6 pg/ml) and FT4 = 3.8 ng/dL (normal, 0.7–1.8 ng/dL).

A ^{131}I thyroid scan after 1.85 MBq showed a multinodular goiter with several nonfunctioning cold areas; ^{131}I thyroid uptake was

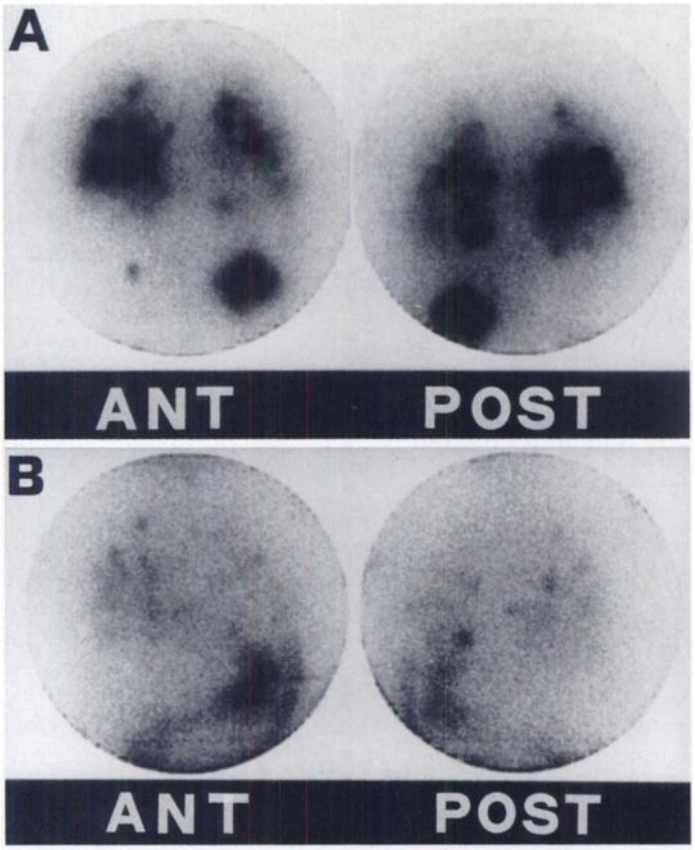

FIGURE 3. (A) Iodine-131 whole-body scan shows radioiodine uptake in pulmonary lesions. (B) Whole-body scan obtained during follow-up after ^{131}I therapy shows significant reduction of pulmonary uptake.

18% at 24 hr and TSI was 4 IU/ml (normal, 1–10 IU/ml). The common causes of hyperthyroidism, namely Graves' disease, toxic nodular goiter (both single or multinodular) and factitious intake of thyroxine, were excluded. Fine-needle aspiration biopsy of a 6-cm nodule was consistent with follicular carcinoma of the thyroid.

The chest radiograph showed multiple macronodular metastases in both lungs, while a 185-MBq ^{131}I whole-body scan revealed ^{131}I uptake in the pulmonary lesions (Fig. 3A). The Tg was 382 ng/mL (normal <85 ng/mL).

A diagnosis of thyrotoxicosis sustained by hyperfunctioning pulmonary metastases was then made. Pretreatment with steroids (methylprednisolone 300 mg/day) and antithyroid drugs (methimazole 60 mg/day) was started to minimize the risk of thyrotoxic storm, and the patient then underwent a total thyroidectomy. The histological diagnosis was consistent with invasive well-differentiated (G1) follicular carcinoma of the thyroid.

An initial improvement in the clinical condition of the patient and of the thyroid functions after surgical therapy lasted for only 1 mo, after which her clinical condition rapidly declined together with a recurrent increase of thyroid hormones (TSH <0.06 mU/liter; FT3 = 7.7 pg/ml; FT4 = 5.4 ng/dL).

Two months after the thyroidectomy, the patient was treated with a total of 9.6 GBq ^{131}I given in two doses with an interval of 6 mo. The most recent follow-up revealed improvement of the metastatic disease with a significant reduction in both the ^{131}I lung uptake (Fig. 3B) and the Tg level (147 ng/mL; 38% of the original value). Two months later, symptoms of hypothyroidism occurred (TSH = 16.9 mU/liter; FT3 = 1.0 pg/ml; FT4 = 0.7 ng/mL) and L-thyroxine replacement therapy (50 μg/day) was started.

DISCUSSION

Thyrotoxicosis is seldom associated with thyroid cancer. The various diagnostic possibilities are presented in Table 1. The most common association is the incidental coexistence of Graves' disease and well-differentiated thyroid cancer; only very rarely is the association due to functioning neoplastic

TABLE 1
Associations of Thyrotoxicosis and Cancer

Thyrotoxicosis	Cancer
A. Thyrotoxicosis and thyroid cancer	
Incidental thyroid cancer (papillary)	Graves' disease (Stimulation of tumor by thyroid-stimulating immunoglobulins)
Incidental microscopic thyroid cancer (papillary)	Graves' disease Multinodular goiter
Incidental thyroid cancer (follicular)	Multinodular goiter Graves' disease
Metastatic thyroid cancer (papillary/follicular)	Bone Lung Lymph nodes Other
Struma ovarii	Benign Malignant Metastatic
B. Thyrotoxicosis and other cancers	
Purely coincidental and unrelated	Many malignant tumors
Pituitary tumors secreting thyroid-stimulating hormone	Usually benign, may be malignant
Tumors secreting human chorionic gonadotropin	
Trophoblastic tumors	Hydatiform mole Choriocarcinoma
Nonthrophoblastic tumors	(Very rare)
Direct tumor invasion or metastatic destruction of thyroid tissue with release of hormone stores	Lymphoma Breast Pancreatic Other

tissue (*5*). Small foci of papillary carcinoma are occasionally discovered incidentally from histology after removal of the thyroid for toxic multinodular or diffuse goiter (*6*). In very rare instances, ovarian teratoma (*7*) (struma ovarii), some trophoblastic tumors (*8–10*) and nonthyroidal cancers (*11–13*) may cause thyrotoxicosis by various mechanisms.

The 2 cases presented here are examples of thyrotoxicosis caused by functioning pulmonary metastases from well-differentiated thyroid carcinomas. Only 54 similar cases, including the 2 described in this article, have been reported since the first description by Leiter et al. (*1*) in 1946. The characteristics of the syndrome were reviewed by Paul and Sisson (*2*).

Our review of the literature reveals that the sex of the patients, age at onset, time elapsed until onset of metastases and the 10-yr survival rate appear to be identical for metastatic follicular carcinoma, with or without coexisting thyrotoxicosis (*2,3,14*). Indeed, almost all of the 54 cases reported had follicular histopathology of the primary and/or metastatic lesions (*2*). In both of our cases, the site of the metastatic disease was the lungs; whereas in the reported cases, bone was the preferential site of metastases (*2,14*). The concomitant diagnoses of thyroid cancer and hyperthyroidism were made in 60% of the cases; in the remainder of the cases, hyperthyroidism occurred between 1 mo and 15 yr (mean, 7.3 ± 4.3 yr) after the initial diagnosis of thyroid carcinoma.

Certain features distinguish these patients, from both a diagnostic and a therapeutic standpoint, from patients with nonhyperfunctioning metastases from differentiated thyroid cancer. First, certain criteria should be met to reach a hyperthyroidism diagnosis due to the overproduction of hormones by metastatic tissue: (a) The exclusion of hyperfunctioning diffuse or nodular thyroid gland; (b) the demonstration of radioiodine uptake by metastatic lesions; (c) low thyroid radioactive iodine uptake; and (d) failure of hyperthyroidism to resolve after adequate thyroidectomy should all be demonstrated (*15*). In both cases reported here, we believe the absence of ophtalmopathy with normal TSI, the scintigraphic appearance of the thyroid gland and low thyroid radioiodine uptake exclude the diagnosis of either Graves' disease or nodular toxic goiter. Iodine-131 whole-body scanning demonstrated that pulmonary metastases were capable of taking up iodine, whereas low thyroid radioiodine uptake was present only in Patient 1, and hyperthyroidism persisted after thyroidectomy in Patient 2. Intense uptake of ^{131}I in the metastases, in spite of the suppressed TSH levels manifested in both our cases, indicates that the bulky pulmonary tumor masses functioned autonomously to cause thyrotoxicosis. The hyperfunction of metastatic thyroid cancer tissue usually is a result of the large autonomous metastatic tumor burden present in these patients or it may be explained by the stimulation of TSH receptors on metastatic cells by TSI in certain cases of concomitant Graves' disease and thyroid cancer.

Second, the therapy of differentiated thyroid carcinoma with hyperfunctioning metastases is aimed at treating both the thyrotoxicosis and the neoplastic disease itself, as both are major causes of morbidity and mortality in these patients. Treatment of the thyrotoxicosis with antithyroid drugs in these patients is often only partially effective, whereas a normalization of hormonal values and prompt clinical recovery can usually be achieved by radioiodine therapy. We observed rapid clinical improvement after ^{131}I therapy in both our cases. In Patient 2, L-thyroxine replacement was required for subsequent hypothyroidism. Radioiodine therapy was also effective in reducing the mass of metastatic pulmonary neoplastic tissue, as confirmed by the decrease in number and size of the metastases depicted by CT, chest radiograph and ^{131}I scintigraphy, as well as by improvement of respiratory function.

No early ill effects were observed after ^{131}I therapy in our patients. The induction of thyrotoxic storm in this condition has been reported as a possible serious and even lethal complication of radioiodine treatment (*4*). It is not related to the dose of radioiodine administered nor can it be reliably predicted by any clinical or biochemical factor (*4,14*). Nevertheless, it seems that thyrotoxic storm is more frequent in seriously ill patients, and it may be prevented by pretreatment with steroids and antithyroid drugs (*4,14*).

To avoid the complication of pulmonary fibrosis, it has been proposed that a maximum of 3 GBq be retained in the lungs at 48 hr (*16*). We administered large fixed doses based on the scintigraphic pattern (focal pulmonary lesions) and the lung uptake (lower than 50% in Patient 1) to reduce the possibility of lung injury (*17*).

The follow-up of patients with metastatic thyroid carcinoma causing hyperthyroidism shows that the overall survival does not differ from that of euthyroid patients with metastatic follicular disease (*14*). Although most patients become hypothyroid, we observed euthyroidism with a normal level of thyroid hormones in Patient 1.

These two cases represent a rare, extreme example of the excessive autonomous biosynthesis and secretion of thyroid hormones by well-differentiated thyroid cancer. Lesser degrees of thyroid hormone biosynthesis and secretion can be detected by the chromatographic analysis of serum (*18–20*) or urine (*21*) for the presence of endogenously labeled thyroid hormones after the administration of ^{131}I for diagnostic whole-body scans or therapy. This technique may serve as an additional technique for monitoring patients with differentiated thyroid cancer (*18, 19*). It may detect the presence of disease even in the absence of a focus on the whole-body ^{131}I scan and is inherently quantifiable (*18–21*).

CONCLUSION

Although thyrotoxicosis due to autonomous, functioning metastatic thyroid cancer is rare, it deserves consideration and recognition. A correct diagnosis is essential for appropriate treatment aimed at resolving the thyrotoxicosis and treating the metastatic disease.

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FDG Imaging of Spinal Cord Primitive Neuroectodermal Tumor

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PET with ^{18}F-fluoro-2-deoxy-glucose (FDG) is well established as an effective imaging modality for evaluating suspected brain tumor recurrence. Use of FDG PET imaging for spinal cord neoplasms has not yet been studied, in large part due to limitations of spatial resolution. One report of FDG PET imaging of brain involvement with primitive neuroectodermal tumor (PNET) demonstrated mild hypometabolism relative to cortical gray matter. We demonstrate with FDG PET imaging the appearance of recurrent intramedullary PNET affecting the cervical spinal cord.

Key Words: PET; spinal cord; neoplasms; primitive neuroectodermal tumor

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PET has been extensively applied to the evaluation of central nervous system (CNS) neoplasms, especially high-grade glial tumors. Tumoral uptake of ^{18}F-fluoro-2-deoxy-glucose (FDG) has been shown to correlate with histological aggressivity and prognosis in both primary and recurrent gliomas (*1–5*). Hypermetabolism has also been variably reported in primary cerebral lymphoma (*6,7*), meningioma (*8*), medulloblastoma (*9*) and non-CNS brain metastasis (*10*). Relatively low glucose metabolic rates have been demonstrated in cerebral involvement with primitive neuroectodermal tumor (PNET) (*9*). Primary spinal cord PNET is uncommon and has not been previously evaluated with PET.

PET rarely has been used to assess neoplastic involvement of the spinal cord primarily due to limitations of spatial resolution and sensitivity. DiChiro et al. (*11*) demonstrated the feasibility of PET imaging with FDG for primary astrocytoma of the spinal cord. Recently, Sasajima et al. (*12*) reported visualization of a spinal cord ependymoma with ^{11}C-methionine and PET. We present the metabolic imaging features of recurrent intramedullary PNET in the cervical spine using FDG and PET.

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CASE REPORT

Patient History

The patient was a 30-yr-old man who was diagnosed with a spinal cord tumor 5 yr earlier when he presented with progressive gait disturbance. MRI of the entire spinal cord and brain was performed at that time and demonstrated extensive patchy areas of abnormal signal and expansion of the spinal cord extending from C-3 to the conus medullaris. Intraoperative biopsy of the lower thoracic spinal cord identified malignant tissue consistent with PNET. Tumor resection was performed with bilateral laminectomies from T7 through L2. The patient then received whole-brain and spine radiation followed by 6 mo of chemotherapy with vincristine and lomustine. The patient's condition remained stable for approximately 4 yr. Serial MRI studies during this interval demonstrated the persistence of mild fusiform dilatation of the cervical spinal cord from C-2 to C-7 with accompanying signal changes and posterolateral and questionable dural enhancement. The patient then presented with a new upper extremity weakness. Repeat MRI of the brain and cervical, thoracic and lumbar spine regions was unchanged with the exception of minimally increased fusiform expansion of the cervical cord and prominence of posterior dural enhancement (Fig. 1). An FDG PET scan was performed to evaluate possible recurrent tumor in the cervical spine.

After the PET scan, which indicated recurrent tumor in the cervical spinal cord, the patient underwent additional radiation treatment of the cervical spine and brain stem areas. The patient steadily deteriorated neurologically and died approximately 1 yr after the PET scan. A limited autopsy confirmed involvement of the cervical spinal cord, as well as corpus callosum, midbrain, medulla and hippocampus, with PNET. Intraventricular tumor was also demonstrated in the lateral ventricles.

PET Imaging

PET imaging was performed on an ECAT ART (CTI PET Systems, Knoxville, TN), which had an in-plane spatial resolution of approximately 6 mm and an axial resolution of 5 mm. The ART comprises two arrays of bismuth germanate block-detectors rotating at 30 rpm, and the scanner had no septa, acquiring and reconstructing data three-dimensionally. The patient was positioned in the scanner with his neck in the 16-cm field of view, and a 15-min transmission scan was performed before intravenous